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ORIGINAL ARTICLE

A comprehensive review and meta-analysis of suPAR as a predictor of acute kidney injury

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Abstract

Introduction and Objective. The global impact of acute kidney injury (AKI) has not been thoroughly investigated. With the development of new techniques, soluble urokinase plasminogen activator receptor (suPAR) has become increasingly important in the diagnosis of AKI. Therefore, a systematic review and meta-analysis was carried out to evaluate the predictive value of suPAR for AKI.

Materials and method. The review and meta-analysis investigated the relationship between suPAR levels and acute kidney injury. Pubmed, Scopus, Cochrane Controlled Register of Trials, and Embase were searched for relevant studies from inception to 10 January 2023. Stata (Ver. 16 StataCorp, College Station, TX, USA) was used for all statistical analyses. A random effects model using the Mantel-Haenszel approach was employed, and odds ratios (OR) and standard mean differences (SMD) with 95% confidence intervals (CI) were calculated for binary and continuous outcomes, respectively.

Results. Nine studies reported suPAR levels among patients with and without AKI. Pooled analysis showed that suPAR levels in patients with and without AKI varied and amounted to 5.23 ± 4.07 vs. 3.23 ±0.67 ng/mL (SMD = 3.19; 95%CI: 2.73 to 3.65; p<0.001). The results from the sensitivity analysis did not alter the direction.

Conclusions. This results show that increasing suPAR levels are associated with the occurrence of AKI. SuPAR might act as a novel biomarker for CI-AKI in clinical practice.

Key words

soluble urokinase plasminogen activator receptor, suPAR, acute kidney injury, acute renal failure, biomarker, prediction, meta-analysis

Abbreviations

AKI – acute kidney injury; **ARF** – acute renal failure; **CI** – confidence interval; **NGAL** – neutrophil gelatinase-associated lipid calin; **NOS** – Newcastle Ottawa Scale; **OR** – odds ratio; **ROS** – reactive oxygen species; **SMD** – standard mean difference; **suPAR** – soluble urokinase plasminogen activator receptor

INTRODUCTION

Acute kidney injury (AKI) is a clinical condition characterized by a rapid (hours to days) decrease in renal excretory function and the accumulation of nitrogen metabolism products, such as creatinine and urea, as well as other clinically unmeasured waste products [1, 2]. Other common clinical and laboratory signs include less urine output (which does not always happen), a buildup of metabolic acidosis, and higher potassium and phosphate [3].

To emphasize that there is a continuum of kidney injury that begins long before sufficient loss of excretory kidney function can be evaluated with routine laboratory testing, the term 'acute kidney injury' in global guidelines has replaced the previously used 'acute renal failure'. AKI can have substantial implications, such as increased morbidity, mortality, and length of hospitalization. For example, AKI has been identified as an independent mortality risk factor in patients treated in intensive care units; therefore, early diagnosis of AKI can be essential in improving the prognosis and treatment of this group of patients. While kidney biopsy, an invasive procedure with possible complications, is not useful and practical in the early identification of AKI, there has been a surge of interest in the use of biomarkers to help in the early diagnosis and management of AKI in recent years. Among others, soluble urokinase plasminogen activator receptor (suPAR) is one such biomarker [4].

SuPAR is a new biomarker that has been found to be an excellent predictor of AKI. It is a protein that a variety of cells, including immune cells, release into the circulation

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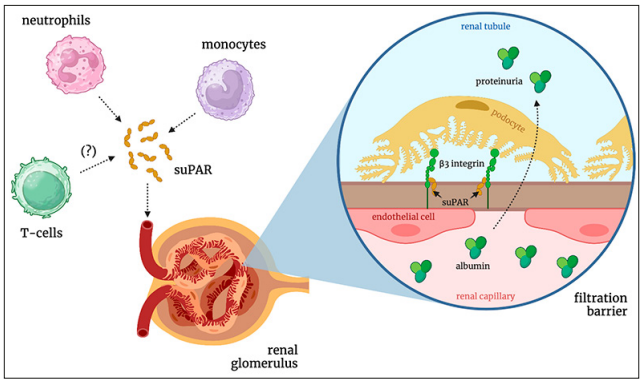

Figure 1. A visualization illustrating the effects of suPAR on the potential development of AKI through the promotion of inflammation, oxidative stress, and apoptosis in the kidneys

and is involved in a variety of physiological processes (Fig. 1). SuPAR levels in the blood of people with AKI have been found to be higher, and the size of this increase has been linked to the severity of the condition [5].

One of the hot spots in kidney disease research in recent years has been the discovery and deployment of new biomarkers for early identification of AKI. A previous study discovered that plasma suPAR was an unanticipated result of neutrophil, monocyte, and macrophage shedding of inflammatory receptors. A mechanistic investigation on kidney disease models indicated that circulating suPAR (derived from inflammatory cells) interacted with v3αvβ3 integrins on podocytes, and that higher plasma suPAR levels might predict nephropathy in otherwise healthy persons and those at risk of chronic kidney disease. SuPAR has been shown to be implicated in the pathogenesis of AKI [6, 7]. The causal pathogenic role of suPAR in the development of AKI was recently substantiated by Nusshag et al., using both clinical data and transgenic mouse experiments [8, 9].

In the context of acute kidney injury (AKI), suPAR has been found to play a significant role in the development of the disease. The levels of suPAR in the blood have been shown to be elevated in patients with AKI, and the extent of this elevation has been shown to be related to the severity of the disease, which suggests that suPAR may contribute to the development of AKI by promoting inflammation [10, 11], oxidative stress [12], and apoptosis in the kidneys [13].

SuPAR has been shown to activate immune cells, including monocytes and neutrophils which play a key role in the development of kidney injury [10]. These immune cells release a number of pro-inflammatory cytokines and chemokines that can damage the kidneys and lead to the development of AKI.

As emphasized previously by the authors, suPAR may contribute to AKI through its effects on oxidative stress, a condition in which there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. ROS can cause oxidative damage to cells and tissues, leading to the development of various diseases, including AKI. SuPAR has been shown to induce oxidative stress in the kidneys, which may also contribute to the development of AKI.

In addition to its effects on inflammation and oxidative stress, SuPAR may also contribute to AKI by promoting apoptosis [12]. Apoptosis is a type of programmed cell death that occurs in response to various stimuli, including injury, inflammation, and oxidative stress [12]. In the context of AKI, SuPAR has been shown to induce apoptosis in kidney cells, which can lead to further damage and the development of the disease.

The presented study aims to evaluate circulating SuPAR as a prognostic marker of acute kidney injury.

MATERIALS AND METHOD

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines were used to carry out this systematic review and meta-analysis [14] (Suppl. Tab. 1). The PROSPERO Registration No. for this systematic review is CRD42023422987.

Data sources and searches. Articles on the relationship of suPAR levels to acute kidney injury were found by searching Pubmed, Scopus, the Cochrane Controlled Register of Trials, and Embase from their inception. The initial searches were conducted on 15 September 2022, and repeated on 20 April 2023. For each database, a specific and effective search method was employed using the following search terms: 'suPAR', 'soluble urokinase plasminogen activator receptor" AND "Acute Kidney Injury" OR "Acute Renal Failure', 'AKI' or

Table 1. Baseline characteristics of included trials

Study	Country	Study design	Acute kidney injury group			No acute kidney injury group			NOS score
			No of patients	Age	Gender, male	No of patients	Age	Gender, male	
Azam et al., 2020	International	Multi-center observational study	91	65(15)	64 (70.3)	261	60(17)	138 (52.9)	9
Gussen et al., 2019	Germany	Prospective single-center non-interventional cohort study	87	NS	NS	27	NS	NS	7
Hayek et al., 2020	USA	Prospective observational cohort study	318	68 (12)	224 (70)	3509	66 (12)	2413 (69)	8
Mossenen et al., 2017	International	Multi-center observational study	21	75 (66-79)	15 (71.4)	86	67 (61-75)	62 (72.1)	8
Qin et al., 2021	China	Prospective study	65	67 (12)	46 (70.8)	334	63 (13)	212 (63.5)	8
Rasmussen et al., 2021	Denmark	Retrospective observational study	327	68 (59-74)	268 (82)	597	67 (59-73)	470 (78.7)	8
Skalec et al., 2022	Poland	Single-centre, prospective observational study	39	69(2)	19 (48.7)	12	60(52)	8 (67)	8
Walls et al., 2021	Denmark	Single centre study	33	75.9 (72.3-83)	8 (24.2)	306	77.9 (70.5-84.5)	119 (38.9)	9
Zhang et al., 2022	China	Case-control study	17	64 (59-69)	13 (76.5)	21	60 (56-66)	13 (61.9)	8

'ARF'. Manual searches were also conducted on the reference lists of the included papers and pertinent systematic reviews. Endnote (X7 for Windows, Clarivate Analytics, Philadelphia, PA, USA) was used to consolidate search results. Duplicates were deleted.

Study selection. All retrieved articles were screened against predetermined selection criteria independently by two investigators (LJ and MP) for the identification of relevant studies. Any differences of opinion were resolved by dialogue with the senior author. Prospective and retrospective observational studies that compared suPAR levels in adult patients, with and without AKI, were included. To avoid overlapping bias in the analysis, only the most detailed report was used when many studies from different institutions included the same groups of people. Moreover, to reduce publication bias, research with a paediatric population, articles with no original data, review papers, conference abstracts or presentations, and editorials or expert opinions were excluded.

Data extraction. Using a predetermined extraction form, three reviewers independently extracted data and evaluated the quality and bias risk of included studies (LJ, MP and AG). The following data was taken from each study: publication data (last name of the first author, year of publication, study design), suPAR levels among patients with and without AKI. When information was uncertain, the authors were contacted. Data from included studies were entered into a pre-defined report form in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Methodological quality and risk of bias assessment. Two authors (LJ and AG) independently evaluated methodological quality and bias risk for publications that satisfied the inclusion criteria. If a decision was contested, a third author served as an adjudicator (LS). The risk of bias within an individual study was determined using the Newcastle Ottawa Scale (NOS) [15] which evaluates the quality of a research study using three criteria: selection, comparability, and exposure. These three variables had maximum scores of 4, 2, and 3, respectively. Studies with NOS scores of 7 were considered high-quality.

Data synthesis and analysis. Stata (Ver. 16 StataCorp, College Station, TX, USA) was used for all statistical analyses. All P values were determined using a two-sided test, and a P value less than 0.05 was considered statistically significant. The incidence of dichotomous data was calculated using the odds ratio (OR) with a 95% CI and analyzed using the Mantel-Haenszel technique. The standard mean difference (SMD) with a 95% confidence interval (CI) was used to represent continuous outcomes. In cases where a research presented a continuous outcome as median, range, and interquartile range, means and standard deviations were approximated using the Hozo et al. method [16].

In all the assessed outcomes, heterogeneity was evaluated by observing forest plots and utilizing I^2 statistics. The I^2 cut-off thresholds of 25%, 50%, and 75% denoted low, moderate, and high degrees of heterogeneity, respectively. If I^2 was greater than 50%, a fixed-effects model was employed; otherwise, a random-effects model was used [17]. Due to the small number of investigations (n<10) a funnel plot was not performed. A sensitivity analysis was performed, in which one research study was withdrawn at a time, and the others were examined to determine the stability and reproducibility of the amalgamated effects.

RESULTS

The PRISMA flow diagram is presented in Figure 2. A literature search of the four databases (PubMed, Embase, Cochrane, and SCOPUS) yielded 355 articles. After removing 181 duplicates, title and abstract screenings of 174 articles was conducted, excluding a further 154. After excluding 11 articles through full text sieving, nine articles were included in the final meta-analyses [6, 18–25].

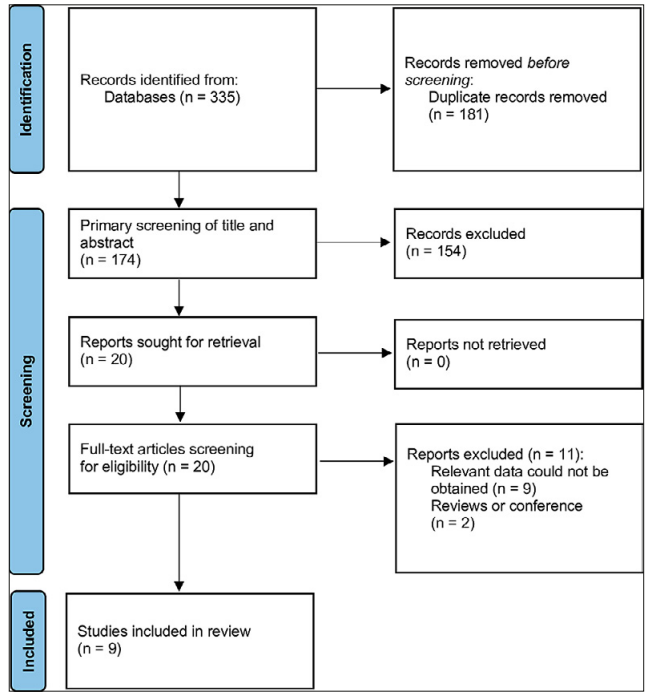

Figure 2. Flow diagram of the search strategy and study selection

The nine trials comprised a combined cohort of 6,151 patients. The participant baseline characteristics of the included studies are shown in Table 1. All selected studies had been published between 2017 – 2022. Of the nine trials, two were performed in Germany and China, and one in each of the following countries: Poland, USA and Denmark. Two studies were international. The NOS scores of the eight included studies were ≥7.

Nine studies reported suPAR levels among patients with and without AKI. Pooled analysis showed that suPAR levels in patients with and without AKI varied and amounted to 5.23(4.07) vs. 3.23(0.67) ng/mL (SMD = 3.19; 95% CI: 2.73 to 3.65; p<0.001) (Fig. 3). The results from the sensitivity analysis did not alter the direction.

DISCUSSION

A systematic and comprehensive meta-analysis that included nine studies was conducted to examine the correlation between suPAR levels and acute kidney injury occurrence. This soluble protein is produced by many different cell types

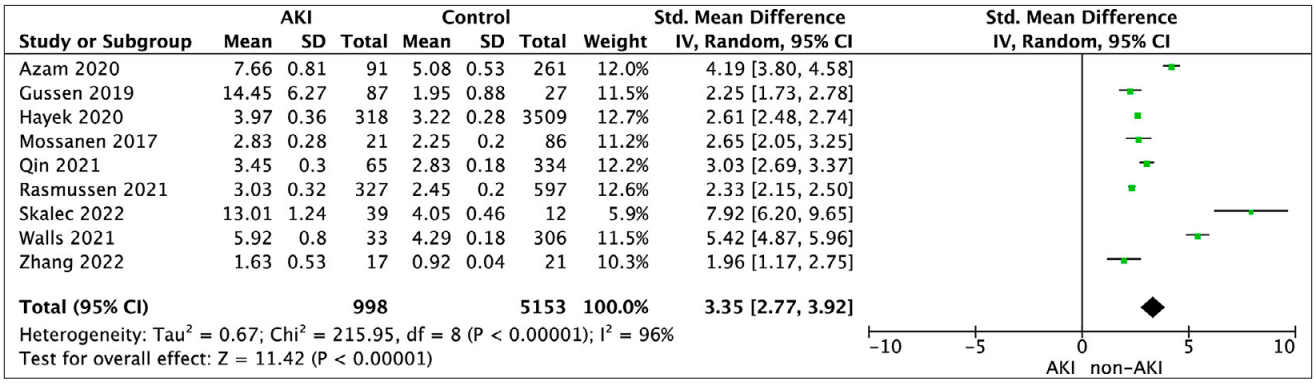

Figure 3. Forest plot of suPAR levels among patients with and without AKI. The centre of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line denotes a 95% confidence interval. The diamonds represent pooled results

and is involved in a number of physiological processes, including inflammation, cell migration and angiogenesis. Studies have shown that elevated levels of suPAR are associated with a variety of diseases, including cancer [26, 27], autoimmune diseases [11, 28], and infectious diseases [29, 30]. In particular, suPAR has been found to be a strong predictor of AKI [31, 32]. The levels of suPAR in the blood have been found to be elevated in patients with AKI, and the extent of this elevation has been shown to be related to the severity of the disease. This is also confirmed by the results obtained in this meta-analysis, which indicate that the level of suPAR closely correlates with the risk of AKI.

SuPAR's high specificity is one of the key reasons it is an excellent predictor of AKI. As indicated by Huang et al., the sensitivity of suPAR in predicting AKI was 0.77 (95% CI 0.67–0.84) and the specificity was 0.64 (95% CI 0.53–0.75) [33]. Moreover, suPAR, unlike other indicators often used to detect AKI, such as creatinine and blood urea nitrogen (BUN), is unaffected by age, muscle mass, or nutrition [34]. As a result, it is a more trustworthy indication of renal function. Furthermore, suPAR has been demonstrated to be higher in individuals with AKI before increases in creatinine or BUN levels are noticed, indicating the start of AKI at an early stage. This early warning is especially important in critically ill patients, who are more likely to develop AKI, and where prompt treatment can make a significant difference in patient outcomes. Moreover, as Azam et al. reported, admission suPAR levels in patients hospitalized for COVID-19 are predictive of in-hospital AKI and the need for dialysis [18]. The prognosis enabling early detection of individuals at risk of developing AKI is highly fascinating and should be one of the focuses of the most recent research on this biomarker. This hypothesis is confirmed by studies that demonstrate that suPAR predicts AKI years before it occurs. Even in acute medical patients with decent eGFR (> 60), if they have a high suPAR, their eGFR is rapidly declining, which shows that suPAR is predictive of eGFR decline [35].

Elevated suPAR levels have been linked to an increased chance of developing AKI as well as a worse prognosis for AKI patients. A study of critically ill patients, for example, discovered that individuals with higher suPAR levels were more likely to need renal replacement treatment, such as dialysis, and had a higher risk of mortality. This emphasizes the need for monitoring suPAR levels in critically ill patients and using the data to guide treatment decisions.

Biomarkers, such as neutrophil gelatinase-associated lipid calin (NGAL), renal injury molecule 1, urine IL 18, and plasma cystatin C, have also been studied and will continue to be studied in AKI [36]. The area under the curve (AUC) for suPAR and NGAL was 0.69 and 0.78, respectively, with no significant difference (p = 0.117). SuPAR in conjunction with NGAL had an AUC of 0.80, which was significantly higher than suPAR alone (p = 0.032) [24]. This further underlines the importance of suPAR and its research in the context of AKI.

SuPAR has been found to be a key predictor of renal recovery in addition to its diagnostic and prognostic significance. SuPAR levels have been reported to decline following the beginning of AKI, and patients with lower suPAR levels are more likely to restore renal function. Monitoring suPAR levels may thus be a valuable tool for directing treatment decisions and measuring the efficacy of therapies targeted at improving renal function.

The first paper on the possible causal role of suPAR in the development of AKI was published by Hayek et al. in 2020 [19]. These data have been corroborated in previous studies [8, 9]. The causal role of suPAR opens new therapeutic possibilities for the prevention and treatment of AKI through the direct targeting of suPAR with biological treatment, e.g., anti-suPAR antibodies, and commercial efforts are pursuing these opportunities.

Despite its great potential, suPAR is not frequently employed in clinical practice as an AKI biomarker. This is due to a number of factors, including the small number of standardized techniques for assessing suPAR levels, and the need for additional validation in larger and more diverse patient groups. Currently, just one firm, 'ViroGates' in Birkoroed, Denmark, has created the sole CE/IVD certified methods for suPAR measurement, which include turbidimetric analysis, suPARnostc turbilatex, and POC tech, which may present major prospects for the future widespread application of this biomarker [37]. Furthermore, the expense of suPAR testing may be prohibitive for some healthcare systems. However, as more research is undertaken and the benefits of employing suPAR as a biomarker are understood, its usage is expected to become more prevalent.

CONCLUSIONS

This systematic review and meta-analysis show that increasing suPAR levels are associated with the occurrence of AKI. SuPAR might act as a novel biomarker for CI-AKI in clinical practice.

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