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Pathogenesis, Biomarkers, and Therapeutic Prospects of Sepsis-Associated Acute Kidney Injury

Wenyue Dong[1,2], Haosen Liu[3], Yang Liu[2]*

[1]College of Clinical Medicine, North China University of Science and Technology, Tangshan 063000, Hebei, China
[2]Department of Critical Care Medicine I, Tangshan Worker's Hospital Affiliated to North China University of Science and Technology, Tangshan 063000, Hebei, China
[3]Department of Critical Care Medicine I, Hebei Medical University, Tangshan Workers' Hospital Affiliated to Hebei Medical University, Tangshan 063000, Hebei, China

**Corresponding author: Yang Liu, 17399702079@163.com*

Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a common critical complication in the ICU, characterized by a complex pathogenesis involving the interplay of multiple factors such as inflammatory imbalance, vascular dysfunction, coagulation disorders, and cellular metabolic abnormalities. Traditional diagnostic indicators like serum creatinine and blood urea nitrogen exhibit lag time, making early identification challenging. In recent years, novel biomarkers have provided new directions for early diagnosis and risk stratification, including tubular injury markers (KIM-1, NGAL, L-FABP), renal function and glomerular injury markers (CysC, sCD35-uEV), cell cycle arrest markers ([TIMP-2] × [IGFBP7]), and inflammatory markers (IL-18, sTREM-1). Currently, supportive therapy remains the mainstay of treatment, encompassing early anti-infection measures, hemodynamic optimization, and timely renal replacement therapy. Novel therapeutic targets addressing the pathogenesis, such as regulating pyroptosis and improving mitochondrial dysfunction, are currently in preclinical and early clinical research stages, offering hope for future specific treatments.

Keywords: Sepsis-associated acute kidney injury; Biomarkers; Pathogenesis; Inflammatory response; Pyroptosis

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1. Introduction

Sepsis-associated acute kidney injury (SA-AKI) is the most prevalent critical complication in the intensive care unit (ICU), with an incidence rate reaching 40–50% [1]. Sepsis stands as the leading cause of AKI, and its renal injury mechanism is complex, involving the interplay of multiple pathophysiological processes such as cytokine storm, microcirculatory disturbances, coagulation disorders, and cell death [2].

Currently, the diagnosis of AKI primarily relies on the KDIGO criteria, which are based on elevated serum

creatinine levels and reduced urine output. However, changes in serum creatinine exhibit a lag time and are susceptible to interference from various non-renal factors [3]. Urine output indicators are also easily influenced by medications and fluid status, leading to delayed diagnosis and patients missing the optimal treatment window [4].

Therefore, the search for highly sensitive and specific biomarkers capable of providing early warning for kidney injury has become crucial for improving the clinical management of sepsis-associated acute kidney injury (SA-AKI) [5]. Meanwhile, a thorough elucidation of the multidimensional pathophysiological mechanism network of SA-AKI, particularly the interactions among core aspects such as inflammatory immune imbalance, microcirculatory disorders, coagulation abnormalities, and programmed cell death, is of paramount importance for developing specific therapeutic strategies that surpass traditional supportive therapies [6,7].

This article systematically reviews the latest research progress on SA-AKI: evaluating the diagnostic value and clinical significance of novel biomarkers; analyzing its complex pathogenesis, with a focus on key aspects such as inflammatory immunity, vascular dysfunction, coagulation disorders, and cellular injury and metabolic reprogramming; summarizing clinical management strategies; and looking ahead to novel therapeutic targets and intervention strategies targeting key pathological mechanisms, providing theoretical and practical guidance for the early identification, timely intervention, and improvement of prognosis for this disease.

2. Biomarkers for sepsis-associated acute kidney injury

Serum creatinine (Scr) and blood urea nitrogen (BUN) are widely used to assess renal function due to their ease of detection and low cost. However, they are influenced by various factors such as age, nutrition, and metabolism, and typically only increase after a significant decline in glomerular filtration rate, making it difficult to achieve early diagnosis and intervention for SA-AKI [1,2]. Therefore, the search for sensitive and specific early biomarkers is imperative. The following is a summary of various novel biomarkers for SA-AKI.

2.1. Renal tubular injury

2.1.1. Kidney injury molecule-1 (KIM-1)

A transmembrane glycoprotein that is highly expressed in the epithelial cells of the proximal renal tubules. After kidney injury, its levels rise faster than serum creatinine (Scr). Studies have shown that urinary KIM-1 begins to increase within 6 hours after patients with sepsis-associated acute kidney injury (SA-AKI) are admitted to the ICU, earlier than the 24-hour change in Scr. Its area under the curve (AUC) for diagnosing SA-AKI is 0.62, making it a superior biomarker to Scr [3,8].

2.1.2. Neutrophil gelatinase-associated lipocalin (NGAL)

A secreted protein with a molecular weight of approximately 25 kDa that is expressed at low levels under physiological conditions but significantly upregulated under pathological conditions such as inflammation and injury. Studies have confirmed the value of urinary, serum, and plasma NGAL in the early diagnosis of SA-AKI. Among them, urinary NGAL exhibits the best diagnostic performance (sensitivity 0.87, specificity 0.84, AUC 0.92) and is considered a novel biomarker for SA-AKI [4,5].

2.1.3. Liver-type fatty acid-binding protein (L-FABP)

A 14 kDa protein primarily synthesized in the liver. During renal tubular ischemia and hypoxia, its excretion in urine significantly increases. Studies have shown that urinary L-FABP has a sensitivity of 0.74 and a specificity of

0.78 for predicting acute kidney injury (AKI), making it a valuable early biomarker for AKI [6].

2.2. Renal function and glomerular injury

2.2.1. Cystatin C (CysC)

A protease inhibitor with a molecular weight of approximately 13 kDa, CysC is stably synthesized in all nucleated cells and is not affected by factors such as age, gender, or muscle mass. In the early diagnosis of sepsis-associated acute kidney injury (SA-AKI), CysC significantly outperforms serum creatinine (Scr), with a sensitivity of 0.84, specificity of 0.82, and an area under the curve (AUC) as high as 0.96 for predicting AKI. Studies have also found that combining CysC with tumor necrosis factor-α (TNF-α) can further enhance diagnostic performance (AUC 0.838) and predict mortality [7].

2.2.2. Single extracellular vesicle CD35 derived from glomerular podocytes (sCD35-uEV)

Professor Linli Lv's team has identified a novel biomarker, sCD35-uEV, which demonstrates excellent diagnostic performance (AUC 0.89) and enables early warning. During the subclinical phase when traditional indicators are abnormal, sCD35-uEV levels have already significantly decreased and are correlated with the severity of injury and prognosis. Research has revealed that podocyte injury is a key mechanism underlying SA-AKI [9].

2.3. Cell cycle arrest

2.3.1. Insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2)

IGFBP7 and TIMP-2 are biomarkers that mediate cell cycle arrest in renal tubular cells. In the early stages of renal injury, both are released by renal tubular cells. The product of their concentrations, [TIMP-2] × [IGFBP7], exhibits excellent predictive value for SA-AKI, with an AUC reaching 0.89 [10]. Combining this indicator with procalcitonin helps identify patients with SA-AKI and those at high risk of short-term adverse outcomes in the intensive care unit (ICU) [11].

2.4. Inflammatory response

2.4.1. Interleukin-18 (IL-18)

As a pro-inflammatory cytokine, IL-18 levels can be detected as elevated in urine within 4–6 hours after the onset of sepsis-associated acute kidney injury (SA-AKI). Studies have shown that urine IL-18 levels in SA-AKI patients in the ICU increase significantly at least 6 hours earlier than serum creatinine (Scr) levels. The diagnostic area under the curve (AUC) after 6 hours is 0.719, which is superior to the 0.677 of Scr, facilitating early prediction of SA-AKI [12,13].

2.4.2. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

A protein of approximately 27 kDa, sTREM-1 is released into the bloodstream and can be excreted in urine during infection and renal injury. Research indicates that sTREM-1 demonstrates early predictive capability 24 hours before the clinical diagnosis of AKI, with AUC values of 0.746 in plasma and 0.778 in urine. Its diagnostic AUC for SA-AKI are 0.794 (plasma) and 0.707 (urine), respectively, and its concentration is positively correlated with the severity of sepsis [14].

3. Pathogenesis of sepsis-associated acute kidney injury

The pathogenesis of SA-AKI is a complex, multidimensional, and dynamically intertwined process involving imbalances in inflammatory and immune responses, vascular dysfunction, coagulation disorders, cellular damage, and metabolic disturbances. These mechanisms mutually reinforce each other, collectively driving the progression of renal injury [15].

3.1. Imbalance between inflammatory and immune responses

During the onset and progression of sepsis-associated acute kidney injury (SA-AKI), the dynamic imbalance between pro-inflammatory and anti-inflammatory responses serves as the core mechanism driving the progression of renal injury. In the early stages of infection, the body simultaneously initiates pro-inflammatory and anti-inflammatory responses to maintain immune homeostasis. On one hand, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate immune cells and renal tubular epithelial cells via Toll-like receptors (TLRs), subsequently activating pathways such as nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinases (MAPKs). This leads to the release of a large number of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and IL-18, forming an "inflammatory storm" that directly damages renal tissue and recruits immune cell infiltration [16–19]. Concurrently, PAMPs/DAMPs can activate the NLRP3 inflammasome, which cleaves gasdermin D (GSDMD) through caspase-1 (classical pathway) or caspase-4/5/11 directly activated by intracellular lipopolysaccharide (LPS) (non-classical pathway), triggering pyroptosis and further amplifying the inflammatory response [19, 20]. On the other hand, the body initiates anti-inflammatory regulation by expressing inhibitory molecules such as inhibitor of kappa B-alpha (IκB-α) and activating mRNA degradation pathways [21]. As sepsis progresses, this fine-tuned regulation becomes imbalanced, resulting in excessive production of pro-inflammatory cytokines and decreased renal clearance capacity. This directly damages renal tubules and microvessels by activating cell death pathways and causing tissue hypoxia [18,22]. In the later stages of the disease, the body experiences "immune paralysis", with comprehensive suppression of immune cell function, increasing the risk of secondary infections. This creates a vicious cycle of "uncontrolled inflammation—immunosuppression—re-infection", continuously exacerbating renal injury [18,22].

3.2. Vascular dysfunction

Vascular dysfunction represents a pivotal aspect in the pathogenesis of sepsis-associated acute kidney injury (SA-AKI), with its core lying in microcirculatory disturbances rather than the traditionally perceived renal ischemia. Studies have demonstrated that during the early stages of sepsis, total renal blood flow may remain normal or even increase; however, microcirculatory disorders and tissue hypoxia constitute the core mechanisms leading to renal injury [23]. Macroscopic vascular dysfunction primarily manifests as abnormal renal blood flow distribution. Postglomerular arteriolar dilation and intrarenal shunting redirect blood from the renal medulla, which has a higher oxygen demand, to the cortex, thereby inducing medullary hypoxia [24]. At the microvascular level, elevated pro-inflammatory cytokines and activated leukocytes during sepsis can trigger microthrombus formation, obstructing renal capillaries, reducing local blood flow, and limiting oxygen diffusion [23]. Concurrently, they promote the generation of reactive oxygen species, further disrupting the epithelial barrier and exacerbating endothelial leakage [23,25]. Dysfunction of renal microvascular endothelial cells plays a particularly crucial role in this process. Shedding of the endothelial glycocalyx is a common pathological alteration in sepsis, accompanied by an increase in soluble

glycocalyx components in plasma [16]. The loss of the glycocalyx facilitates leukocyte leakage and platelet adhesion while reducing blood flow velocity, potentially leading to microthrombus formation and capillary obstruction [16]. Molecular mechanisms such as the vascular endothelial growth factor/receptor 2 complex, the angiopoietin-Tie2 system, and the sphingosine-1-phosphate/its receptor 1 signaling pathway have all been confirmed to participate in regulating the increased renal microvascular permeability observed in sepsis [26,27].

3.3. Coagulation dysfunction

In the state of sepsis, an imbalance occurs between the coagulation system and the anticoagulation system. Endothelial injury and inflammatory responses further amplify this imbalance, exacerbating renal injury [28]. Sepsis rapidly induces an increased expression of procoagulant factors (such as thrombin and tissue factor) within the kidneys, leading to the deposition of fibrin in the glomeruli and microvasculature. Concurrently, microvascular endothelial cells upregulate the expression of protease-activated receptor 2, amplifying procoagulant signals [29,30]. The weakened or ineffective function of the anticoagulation system further exacerbates the coagulation-anticoagulation imbalance. The quantity of endogenous anticoagulant substances decreases, and antithrombin undergoes accelerated degradation due to increased neutrophil elastase, significantly shortening its half-life; activated protein C (APC), which possesses both anticoagulant and anti-inflammatory properties, also experiences downregulated expression [31,32]. Additionally, the formation of anticoagulant complexes is hindered. APC requires the synergistic action of endothelial protein C receptor (EPCR) and thrombomodulin (TM) to exert its anticoagulant effects. EPCR promotes the activation of protein C by the thrombin-TM complex, maintaining an anticoagulant state [33]. During sepsis, the protein levels of EPCR and TM in the kidneys decrease by more than 50%, reducing the formation of anticoagulant complexes and inducing a procoagulant state; simultaneously, the levels of soluble EPCR and TM in the circulation increase, while plasma APC levels decrease, further weakening the body's anticoagulant capacity [30,34].

3.4. Cellular injury and metabolic disorders

3.4.1. Pyroptosis

Pyroptosis is a form of programmed cell death distinct from apoptosis and necrosis, playing a significant role in the pathogenesis of sepsis-associated acute kidney injury (SA-AKI) [35,36]. The essence of pyroptosis is triggered by the activation of inflammasomes, relies on Caspase-mediated processes, and ultimately leads to cell membrane perforation and rupture, releasing a large number of inflammatory factors [37,38]. In SA-AKI, pyroptosis is mainly achieved through the core pathways of classical and non-classical routes: In the classical pathway, inflammasomes such as NLRP3 recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and subsequently activate Caspase-1 [39,40], which then cleaves the GSDMD protein to form membrane pores and promotes the maturation and release of IL-1β and IL-18 [41–43]. The non-classical pathway directly activates Caspase-4/5 or Caspase-11 through intracellular lipopolysaccharides (LPS), inducing GSDMD cleavage and triggering pyroptosis [44,45]. Gene knockout studies have demonstrated that inhibiting Caspase-1/11 can significantly alleviate sepsis-induced kidney injury [46,47].

In addition to the aforementioned core pathways, Z-DNA binding protein 1 (ZBP1) exacerbates pyroptosis-related cell death by recognizing damage signals, thereby intensifying inflammatory death in renal tubular epithelial cells [48-50]. The activation of the NF-κB pathway provides essential preparation for inflammasome assembly [51,52]. Meanwhile, oxidative stress resulting from excessive production of mitochondrial reactive oxygen

species can directly activate NLRP3, forming a vicious cycle that exacerbates kidney injury [53–55].

3.4.2. Apoptosis

As a form of programmed cell death, apoptosis serves as a crucial mechanism for maintaining intracellular homeostasis in sepsis-associated acute kidney injury (SA-AKI). During the early stages of SA-AKI, renal tubular epithelial cells undergo inflammation, oxidative stress, and ischemia-reperfusion injury, leading to excessive apoptosis in a large number of cells [56]. Apoptosis occurs through the combined action of endogenous and exogenous pathways. The endogenous pathway involves the opening of mitochondrial permeability transition pores, the release of cytochrome c, the activation of caspase-9, and subsequently caspase-3, initiating the apoptotic cascade. The exogenous pathway is triggered by the binding of Fas to FasL, activating caspase-8, which ultimately also acts on caspase-3 [57,58]. Studies have shown that caspase-3 deficiency can reduce apoptosis in microvascular endothelial cells and renal tubular ischemia in mice with AKI, suggesting its central role in SA-AKI [59]. Furthermore, pharmacological inhibition of caspase-3 expression significantly improves the survival rate of mice with SA-AKI [60].

3.4.3. Mitochondrial dysfunction and energy crisis

The kidney, as a highly metabolic organ, is rich in mitochondria, and its functional status directly affects the survival of renal cells. In SA-AKI, mitochondrial dysfunction manifests as reduced ATP production and accumulation of reactive oxygen species, further inducing mitochondrial membrane potential collapse and cytochrome C release, promoting apoptosis and inflammation [61]. Additionally, mitophagy is a crucial process for clearing damaged mitochondria, and its dysregulation can lead to the accumulation of reactive oxygen species (ROS) and cell death [62]. PGC-1α, a key regulator of mitochondrial biogenesis, exhibits decreased expression in sepsis-associated acute kidney injury (SA-AKI), with its levels inversely correlated with the severity of renal injury [63]. Therefore, restoring mitochondrial function has emerged as a potential therapeutic target for SA-AKI.

3.4.4. Metabolic reprogramming and energy depletion

SA-AKI is accompanied by significant metabolic reprogramming. During the early stages of sepsis, the body initiates transcriptional and translational responses to combat infection, a process that is highly energy-consuming. As the disease progresses, cells enter a “shutdown phase”, characterized by global translational suppression, with eIF2α phosphorylation serving as a key mechanism [21]. While this translational shutdown aids in energy conservation, prolonged suppression becomes pathological, hindering repair [64]. Studies have shown that the use of ISRIB or overexpression of GADD34 can reverse translational suppression and promote renal function recovery [65]. Furthermore, polyamine metabolism plays a crucial role in renal injury repair, with A-to-I RNA editing of AZIN1 enhancing polyamine synthesis and promoting metabolic adaptation and tissue repair [66].

4. Prospects for the treatment of sepsis-associated acute kidney injury

SA-AKI involves complex pathophysiological mechanisms, and currently, there are no specific therapeutic interventions available, with clinical management primarily relying on supportive care [67]. Early identification and intervention are key to improving outcomes, including timely antimicrobial therapy, hemodynamic optimization, and avoidance of nephrotoxic drugs [68].

Supportive therapy is based on controlling the source of infection and optimizing hemodynamics. According

to guidelines, broad-spectrum antibiotic therapy should be initiated within 1 hour [69]. For patients with tissue hypoperfusion or shock, it is recommended to start resuscitation with 30 ml/kg of crystalloid solution and adjust based on fluid responsiveness [70]. Although there is controversy regarding the type of crystalloid solution, existing evidence indicates that normal saline does not significantly increase the risk of acute kidney injury (AKI) when the total volume does not exceed 4 liters [71]. Norepinephrine is the preferred vasoactive drug, with the goal of maintaining a mean arterial pressure (MAP) > 65 mmHg. Patients with a history of hypertension may require a higher target (e.g., > 85 mmHg) to reduce the progression of AKI and the need for renal replacement therapy [72,73].

Novel biomarkers are helpful for early identification and risk stratification. Traditional indicators such as serum creatinine and urine output exhibit a lag in sepsis [74]. In contrast, urine [TIMP2] · [IGFBP7] demonstrates good performance in predicting severe AKI, while plasma neutrophil gelatinase-associated lipocalin (NGAL) can indicate tubular injury before creatinine levels rise [75,76]. Proenkephalin (penKid) levels are associated with mortality and aid in identifying subclinical AKI [77]. Renal resistive index (RRI) allows for bedside assessment of renal perfusion, but its value in predicting the persistence of AKI is limited [78].

Regarding renal replacement therapy (RRT), evidence does not support its early prophylactic use [79]. Initiation should be based on clear indications such as refractory fluid overload, severe electrolyte disturbances, or acidosis [80]. It is recommended that the dose of continuous RRT be set at 20–25 mL/kg/h, and the target for intermittent dialysis be a weekly Kt/V of 3.9 [81]. For patients with hemodynamic instability, continuous RRT may offer advantages, but the choice of modality should be individualized [82].

In research on novel therapeutic targets, angiotensin II has been shown to improve hemodynamics and reduce the need for RRT in patients with refractory shock [83]. Recombinant alkaline phosphatase demonstrates renal protective potential through the dephosphorylation of endotoxins [84]. Inhibitors targeting the pyroptosis pathway (such as NLRP3/caspase-1/GSDMD), including MCC950 and VX-765, have exhibited protective effects in preclinical studies [46,85]. Phytochemicals like curcumin have also demonstrated therapeutic value in experimental models through multiple mechanisms [19].

5. Summary

Sepsis-associated acute kidney injury (SA-AKI) remains a significant clinical challenge in critical care medicine. Despite increasing research into its pathophysiological mechanisms, specific targeted treatment options are still lacking in clinical practice. Reviewing relevant research progress, the main conclusions are as follows.

The key to early diagnosis and risk stratification lies in the application of novel biomarkers. Traditional indicators such as serum creatinine and urine output exhibit significant lag, whereas novel biomarkers (e.g., NGAL, CysC, [TIMP-2] × [IGFBP7], etc.) can provide early warnings of renal injury and offer crucial evidence for precise risk stratification, thereby compensating for the deficiencies of traditional indicators.

The pathogenesis of sepsis-associated acute kidney injury (SA-AKI) is characterized by multidimensional and dynamically intertwined processes, involving multiple aspects such as inflammatory and immune imbalance, vascular dysfunction, coagulation system disorders, cellular damage, and metabolic disturbances. Among these, pyroptosis mediated by the NLRP3 inflammasome/Caspase-1/GSDMD pathway serves as a core hub connecting infection signals to renal injury, playing a pivotal role in the onset and progression of the disease.

Currently, clinical treatment primarily relies on supportive care, emphasizing timely infection control and optimized hemodynamic management. The initiation of renal replacement therapy should be based on clear

clinical indications rather than early preventive application, and treatment plans need to be tailored individually.

The hope for future treatment lies in targeted therapies addressing key pathogenic mechanisms. Inhibitors targeting the pyroptosis pathway, as well as drugs such as angiotensin II and alkaline phosphatase, have demonstrated protective potential in research, while multi-target natural compounds like curcumin warrant further exploration.

Overall, the clinical management of sepsis-associated acute kidney injury (SA-AKI) is shifting from passive support to a precision medicine model based on early warning and targeted interventions. In the future, efforts should focus on promoting the clinical application of novel biomarkers, accelerating the clinical translation of targeted drugs, and exploring individualized treatment strategies to break through the current therapeutic status quo of SA-AKI and improve patient prognosis.

Disclosure statement

The authors declare no conflict of interest.

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