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Review

Research status of pathophysiological mechanisms and biomarkers of sepsis-associated acute kidney injury

Xiaobei Zhang†, Min Wang†, Yi Zhang, Xuelin Li, Xiangcheng Zhang*

Department of Critical Care Medicine, Huai'an First Hospital, Nanjing Medical University, Huai'an 223300, China
*** Corresponding author:** Xiangcheng Zhang, zhxc0318@163.com
† These authors contributed equally to this work.

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Abstract: Sepsis is a life-threatening condition triggered by infection. According to the 45th Critical Care Medicine Sepsis 3.0 criteria, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated immune response to infection. Renal injury is a common manifestation of organ dysfunction in this setting. Acute kidney injury (AKI) that develops within seven days of a sepsis diagnosis is classified as sepsis-associated acute kidney injury (SA-AKI). Earlier studies proposed that renal damage during sepsis was primarily attributed to insufficient renal blood flow. However, more recent experimental and clinical evidence suggests that renal blood flow often remains stable or even increases during sepsis. As a result, reduced renal blood flow is no longer considered the primary mechanism underlying AKI. Current research efforts are increasingly focused on elucidating the roles of immune dysregulation, inflammatory cascades, coagulation abnormalities, and metabolic reprogramming in the pathogenesis of sepsis. The identification of novel kidney stress and injury biomarkers has also advanced risk prediction and early diagnosis of acute kidney injury in the context of sepsis. This paper primarily reviews the pathophysiological mechanisms and early diagnostic biomarkers of sepsis-associated acute kidney injury from a cellular perspective, aiming to enhance clinicians' understanding of this condition and improve patient outcomes.

Keywords: sepsis; sepsis-associated acute kidney injury; pathophysiologic mechanisms; therapeutic strategies; cells; biomarker

1. Introduction

Sepsis is one of the most prevalent conditions among ICU inpatients, characterized by high incidence and mortality rates. In China, there are approximately 4.8 to 6.1 million hospitalized sepsis patients annually, with older adults over 65 years accounting for about 57.5% of cases and children under 10 years comprising more than 20% [1]. Sepsis-associated acute kidney injury (SA-AKI) is defined as AKI occurring within seven days after a diagnosis of sepsis and requires meeting both the Sepsis 3.0 (Sepsis 3.0) diagnostic criteria [2] and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI [3].

Initially, SA-AKI was thought to be mainly due to decreased renal blood flow and insufficient perfusion, which caused kidney damage. However, more recent studies indicate that early septic shock is predominantly characterized by a hyperdynamic state with systemic vasodilation, and renal blood flow in patients with SA-AKI is not significantly reduced and may even increase [4,5]. Furthermore, it has been observed that AKI incidence is not disproportionately higher in patients who survive cardiac arrest compared to other types of shock [6]. Current research suggests

that renal dysfunction in sepsis is associated with a variety of factors, including immune dysregulation, pyroptosis, inflammatory cascades, endothelial dysfunction, mitochondrial impairment, microthrombus formation, and coagulation abnormalities. These mechanisms often interact and exacerbate one another, contributing to a poor prognosis.

This complexity makes it challenging to pinpoint the exact onset of kidney damage, which hinders timely intervention and prevention. Thus, a comprehensive understanding of its pathophysiological mechanisms and the development of methods for early detection are critical to providing effective supportive care and mitigating further harm.

This review explores the current definitions, epidemiology, pathophysiological mechanisms, and advancements in early diagnostic biomarkers for SA-AKI. By synthesizing findings from multiple studies, this paper outlines the protective and injurious mechanisms involved in the progression of SA-AKI. It aims to offer new perspectives for early clinical recognition and intervention, ultimately improving outcomes for patients with this condition.

2. Risk factor analysis

Risk factors for SA-AKI include age, gender, smoking history, comorbidities, infectious agents, and the use of vasopressin and other vasoactive drugs. Among these, obesity and comorbidities such as hypertension and diabetes mellitus are the most common contributors to AKI. A previous risk factor analysis involving 206 ICU patients diagnosed with sepsis, excluding those with pre-existing chronic kidney disease, cirrhosis, or thrombocytopenia, revealed a significantly higher incidence of AKI in obese patients, those with diabetes, and those with concomitant thrombocytopenia [7].

Additionally, a subgroup analysis within a meta-analysis identified heterogeneity in the sources of infection across different populations. Pulmonary infections were the most frequent source of SA-AKI among the Chinese population [8], followed by comorbidities such as chronic kidney disease (CKD), cardiovascular diseases, and liver diseases. In patients with comorbid CKD, renal dysfunction in SA-AKI tends to be more severe and challenging to reverse, highlighting the critical role of pre-existing renal health in the progression and prognosis of SA-AKI.

3. Pathophysiological mechanisms

3.1. Dysregulation of the immune response

Immune dysfunction is key to the development of sepsis, with hyperimmunity leading to overreactive injury and immunosuppression leading to weakened defences. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) initiate an inflammatory cascade reaction by binding to pattern recognition receptors (PRRs), leading to the release of a large number of inflammatory mediators (vasoactive amines, arachidonic acid metabolites, cytokines, platelet-activating factor, substance P), which activate the pattern recognition receptor on the immune cells and initiate an immune response, and inflammation. At the initial stage,

local tissue cells lose their function and undergo apoptosis, and the apoptotic cells are phagocytosed and cleared, which also promotes the release of growth factors and anti-inflammatory factors, which helps to inhibit the inflammatory response. At this time, the pro-inflammatory and anti-inflammatory aspects of the body are in a dynamic equilibrium. However, as the disease progresses, the immune system is over-activated due to excessive inflammation and organ dysfunction, large numbers of lymphocytes are depleted, and antigen-presenting cells are reprogrammed, leading to the onset of immunosuppression [9,10].

Cellular pyroptosis, different from apoptosis, is an immune-stimulated programmed cell death that produces local and systemic effects by releasing inflammatory mediators and recruiting immune cells, which can activate the body's inflammatory response in the early stages of the disease. With the progression of the disease, many cells are destroyed, releasing excessive pro-inflammatory factors and chemokines. Excessive cellular pyroptosis may lead to the release of DAMPs and pro-inflammatory factors, triggering the overexpression of other pro-inflammatory factors and causing necrosis of renal tubular cells. The necrosis of renal tubular cells can also trigger the release of DAMPs, further exacerbating inflammation. This process leads to the gradual accumulation of the entire inflammatory process and the cascading of layers, forming a vicious circle that leads to a cytokine storm [9,11–13].

Immunosuppression in sepsis is also associated with overproduction of anti-inflammatory factors, including IL-4, IL-10, IL-33, and IL-35. IL-4 promotes the differentiation of CD4+ T cells to Th2 cells and promotes the release of anti-inflammatory factors while suppressing the release of pro-inflammatory factors. IL-10 can inhibit the secretion of pro-inflammatory factors and promote the differentiation of myeloid-derived suppressor cells (MDSCs) to regulatory cells (Tregs) [10]. Among them, macrophages are the core mediators of sepsis-associated kidney injury; when the body is in an immune disorder, macrophages may lead to both hyper-immunity through the release of pro-inflammatory factors and immunosuppression through the release of anti-inflammatory factors. In the early stage of AKI, macrophages are activated and up-regulate the M1 phenotype, and the M1 phenotype of macrophages expresses inducible nitric oxide synthase (iNOS) and secretes pro-inflammatory factors [14]. A study observed that CLP-induced sepsis in a mouse model of sepsis showed significant macrophage aggregation in its renal tissue sections after 24 h. The iNOS mRNA expression level line was significantly higher than the control group's. iNOS mRNA expression was higher in M1-type macrophages, and M1 macrophages secreted pro-inflammatory factors (TNF-α, IL-6, IL-1β, IL-23, IL-12), chemokines (CXCL2, CCL8, CXCL4) and reactive oxygen species (ROS), exacerbating renal impairment [15]. As the disease progresses, the M2 phenotype is manifested in the later stages. M2-type macrophages stimulate tubular cell proliferation, downregulate nitric oxide synthase, and secrete high levels of anti-inflammatory factors (IL-10, arginase-1, CCL24, CCL22, CCL17) [14,16]. The resident macrophages of the kidney are MHCII-F4/80hi macrophages and CD11bhi macrophages, of which F4/80hi macrophages are the major immunomodulatory cells and have a protective role in SA-AKI. The experimental group of a recent study selectively depleted F4/80hi macrophages by injecting diphtheria toxin into mice, and then injected the experimental group (F4/80hi) with diphtheria toxin, and then injected

the experimental group (F4/80hi) with diphtheria toxin, and then injected the experimental group (F4/80hi) with diphtheria toxin. The experimental group (F4/80 MWT mice) and the control group (F4/80 MKO mice) were subjected to CLP-induced sepsis, and it was observed after 24 h that the experimental group exhibited more severe sepsis and higher IL-6 levels compared to mice not injected with diphtheria toxin. It is because F4/80hi macrophages express IL-1 receptor antagonists that limit IL-6 expression in renal endothelial cells, thus limiting the progression of SA-AKI. In this experiment, it was also found by treating both groups of mice with anabolic diphtheria toxin, a recombinant human IL-1 antagonist, that, compared to F4/80hi macrophage-depleted F4/80 MWT mice, renal function was reversed in F4/80 MKO mice [17]. This therapeutic regimen of selectively blocking IL-6 production has the opportunity to serve as a new targeted therapy to reverse renal impairment during sepsis. As the disease progresses, macrophages are progressively depleted, and their excessive apoptosis leads to immunosuppression and impaired clearance of metabolic waste products from the body, resulting in increased renal injury and systemic inflammatory response.

3.2. Endothelial dysfunction

Endothelial cells are involved in substance transport, glomerular filtration, regulation of the microenvironment and other processes, and they can respond rapidly to injury by sensing changes in blood pressure and blood flow. The endothelial surface expresses various molecular receptors (TLR, NOD-like receptors), which can interact with various cellular cytokines, chemokines, adhesion molecules and other inflammatory mediators, and activated neutrophils, platelets, and other cellular targets. Receptors interact and synergize in the body's inflammatory response [18].

During acute inflammation, endothelial cell apoptosis, intercellular adhesion molecule damage and glycocalyx catabolism lead to increased endothelial permeability, interstitial oedema, and aggravated circulatory disturbances, in which the endothelial glycocalyx (eGC), as a key regulator of the integrity of the vascular endothelial barrier, is a layer of glycosaminoglycan polymers adhering to proteoglycans on the surface of the endothelial cells. Axel Nelson et al., in patients with septic shock arterial blood, significantly increased frontal eGC levels were detected in the arterial blood of patients with septic shock, and eGC levels were correlated with mortality [19]. Inflammatory mediators induce the activation of the inflammatory cascade, glycocalyx catabolism and shedding, and adhesion molecules on the surface of endothelial cells are exposed, and the shedding of adhesion molecules, such as E-selectin and ICAM-1, can be detected in the plasma of patients with sepsis. Their levels correlate positively with the severity of the disease [20,21]. In addition, exposure to adhesion molecules can further exacerbate inflammation, fibrin formation and thrombosis, microvascular dysfunction, and multiorgan dysfunction due to localized recruitment of platelets and neutrophils. Glycocalyx levels reflect the extent of endothelial damage in sepsis. A study by Kataoka, Hanae DDS et al. found that the endothelial glycocalyx structure was disrupted or even disappeared from the capillaries in a mouse model of sepsis, with a thinning of the vascular endothelial cell layer and a higher vascular permeability. It was also observed

that due to the disruption of glycocalyx structure, the leukocytes' adhesion with the endothelium of the blood vessels was increased, and also the endothelial release of plasminogen inhibitor 1 (PAI-1) and an increased risk of microthrombosis. Once microthrombi form, the kidney suffers localized ischemic hypoxic injury [22].

3.3. Mitochondrial dysfunction

The kidneys, being metabolically demanding organs with a high density of mitochondria, rank second in mitochondrial content among all organs. During the early stages of sepsis, mitochondrial quality control relies on mitochondrial autophagy, a selective process that removes damaged or dysfunctional mitochondria. Initially, mitochondrial autophagy acts as a compensatory mechanism, protecting organs from inflammation. However, as sepsis progresses, autophagic proteins become depleted, failing to counteract inflammation effectively. The accumulation of damaged organelles within cells leads to necrosis and further exacerbates tissue injury.

In sepsis, the body enters a hypermetabolic state, where inflammatory mediators directly impair the electron transport chain, causing mitochondrial oxidative stress. Proximal tubule cells shift from OXPHOS to glycolysis, converting pyruvate to lactate. This metabolic reprogramming significantly reduces ATP production efficiency while increasing reactive oxygen species (ROS) generation [23]. ROS damage mitochondrial proteins and DNA, further impairing mitochondrial function and amplifying inflammation by activating pathways such as NF-κB. Research indicates that patients with sepsis-associated acute kidney injury (SA-AKI) exhibit reduced mitochondrial DNA (mtDNA) levels, decreased mitochondrial integrity, and diminished mitochondrial mass in renal tissues compared to patients with non-septic AKI. These deficiencies contribute to inadequate renal energy supply and worsen kidney injury [24,25].

Experimental interventions targeting ROS removal from mitochondria have demonstrated promising outcomes, including improved early renal perfusion, restored ATP levels, and reduced apoptosis and necrosis in renal tubular cells [26].

Proteomic studies of kidney tissues in SA-AKI mice revealed significant alterations in protein expression. Compared to controls, the SA-AKI group exhibited 353 upregulated and 166 downregulated proteins. The downregulated proteins were predominantly associated with mitochondrial proteins, respiratory chain complexes, and oxidoreductases. Processes such as oxidative phosphorylation, lipid metabolism, amino acid metabolism, and glycan metabolism were notably suppressed, reflecting sustained metabolic reductions. These metabolic impairments were associated with cell cycle arrest and exacerbation of renal injury [27].

Furthermore, external factors in sepsis, including altered hormone levels, antibiotic use, and catecholamines, can directly inhibit mitochondrial function. This inhibition decreases ATP levels, disrupting the metabolic energy supply and compounding renal dysfunction.

3.4. Coagulation disorders

In sepsis, the coagulation system becomes excessively activated, leading to depletion of coagulation factors. This process is exacerbated in the presence of hepatic

dysfunction or vitamin K deficiency, which further reduces the synthesis of coagulation factors. Additionally, inflammatory conditions disrupt the regulation of coagulation by impairing the synthesis, depletion, and destruction of coagulation inhibitors. Chronic inflammatory stimulation contributes to dysfunction in the activated protein C system, reducing the inactivation of coagulation factors Va and VIIIa, which results in excessive thrombin generation and platelet aggregation.

Moreover, the inflammatory state promotes the accumulation of fibrin due to elevated production of plasminogen activator inhibitor-1 (PAI-1) and suppression of the endogenous fibrinolytic system. These events culminate in systemic coagulation disorders, heightened thrombotic risk, and exacerbation of localized ischemic-hypoxic injury to the kidneys.

In sepsis, extracellular vesicles (EVs) play a significant role in transporting procoagulant factors. Numerous studies have demonstrated that EVs carry tissue factors and phosphatidylserine (PS) on their surface. Phosphatidylserine, an anionic phospholipid, is typically exposed on injured cells and their derived microparticles, providing binding sites for leukocytes, thrombospondin, and tenase complexes. This exposure induces thrombin production and enhances the release of pro-inflammatory factors in a dose-dependent manner through interactions among blood cells, endothelial cells, and circulating microparticles, resulting in strong procoagulant and pro-inflammatory activities [28–30].

Therapeutic strategies targeting PS have shown promise. For example, the endogenous protein annexin A5 (ANXA5) homodimer Diannexin (DA5) can bind to PS, preventing its exposure. This intervention has been demonstrated to reduce renal tubular injury, limit leukocyte infiltration, and improve renal function in septic models [31].

Additionally, pathogen-associated molecular patterns (PAMPs) activate the inflammatory response, triggering endothelial cell activation, deposition of neutrophil extracellular traps (NETs), neutrophil migration, and tissue factor release. These events further activate the coagulation cascade and promote immunothrombosis. Damage to the endothelial barrier by inflammatory mediators inactivates ADAMTS-13, a metalloprotease responsible for cleaving von Willebrand factor. This inactivation is exacerbated by thrombin, clotting products, granulocyte elastase, and reactive oxygen species (ROS), increasing the risk of acquired ADAMTS-13 deficiency and disseminated intravascular coagulation (DIC) [18,32]. DIC, a severe complication in sepsis, significantly contributes to its high mortality rate.

3.5. Metabolic reprogramming

During sepsis, body cells undergo metabolic reprogramming, primarily characterized by the suppression of mitochondrial oxidative phosphorylation and the upregulation of glycolysis. This metabolic shift is advantageous during mild inflammation, as enhanced glycolysis supplies the biosynthetic precursors and energy required for immune cell proliferation and function. However, moderate metabolic reprogramming amplifies the inflammatory response in SA-AKI. Excessive activation of immune cells and the subsequent release of large quantities of pro-inflammatory factors can even result in a cytokine storm.

Renal tubular injury is a critical aspect of SA-AKI, with renal proximal tubule cells (RPTCs) playing a central role in tubular reabsorption and consuming significant amounts of energy. Under normal physiological conditions, nearly all the energy required by RPTCs is derived from mitochondrial fatty acid β-oxidation. However, in SA-AKI, mitochondrial dysfunction impairs fatty acid β-oxidation, leading to a metabolic shift toward glycolysis.

In a study conducted by Joshua A. Smith et al., LPS-induced changes in glucose metabolism were evaluated in the renal cortex of a mouse model of SA-AKI. The study found that LPS rapidly increased hexokinase activity through the EGFR/PI3K/Akt-dependent signaling pathway. However, this activation alone was insufficient to enhance glycolysis in the renal cortex; instead, the metabolic shift was achieved through the upregulation of the pentose phosphate pathway [33]. Although metabolic reprogramming of RPTCs provides an immediate energy supply to the kidney in the short term, prolonged glycolysis may lead to immunosuppression, permanent renal atrophy, and fibrosis in tubular epithelial cells (TECs), thereby increasing the risk of progression from AKI to CKD [34,35].

Furthermore, increased expression of key glycolytic enzymes in renal tubular epithelial cells has been shown to elevate glycolysis and lactic acid production, creating a hypoxic and acidic microenvironment. This environment inhibits podocyte proliferation and differentiation, exacerbating renal fibrosis [36].

4. Biomarkers for early warning of acute kidney injury in sepsis

The occurrence of sepsis can lead to septic shock, multiple organ failure, and kidney damage. When septic shock occurs in sepsis patients, the probability of renal failure is higher [37]. Early warning and timely correction of S-AKI can effectively improve the prognosis of S-AKI patients at the early stage of onset. Although the gold standard for the diagnosis of AKI is still based on elevated serum creatinine concentration and/or decreased urine output. But as with other types of AKI, serum creatinine may be an insensitive indicator of kidney injury, and hypouria may be nonspecific in S-AKI, so there is an optimal opportunity for early S-AKI treatment to be lost based on changes in blood creatinine and urine volume. In recent years, studies have found that a variety of novel biomarkers may be important for the early diagnosis and prediction of S-AKI prognosis, which can predict the occurrence of AKI in advance and evaluate the prognosis, so as to conduct early intervention and treatment, and reduce the incidence and mortality of SIAKI. Currently, new biomarkers widely accepted include: Neutrophil gelatinase-associated lipid carrier protein (NGAL), liver fatty acid binding protein, interleukin-18 (IL-18), urinary kidney injury molecule 1 (KIM-1), cell cycle arrest biomarker, cystatin C (CysC), etc.

Studies have shown that in animal models of ischemic or nephrotoxic renal damage, the secretion of NGAL in renal tubular epithelial cells increases rapidly, and the concentration in urine is more than 10 times that in blood [38,39]. Studies have shown that compared with other types of AKI, the detection rate of NGAL in plasma and urine of S-AKI patients is higher [40]. Zhang et al. [41] demonstrated through systematic review and meta-analysis [42]. With the publication of a large number of

new research results, an updated systematic review and meta-analysis are needed to evaluate the diagnostic and prognostic value of NGAL in S-AKI.

Kidney Injury Molecule-1 (KIM-1) KIM-1 is a 38.7kDa transmembrane tubular glycoprotein with extracellular immunoglobulin domain and intracellular tyrosine protease phosphorylation signaling protein [43]. A meta-analysis showed that urinary KIM-1 was a good predictor of AKI (area under the curve 0.86, sensitivity 74%, specificity 86%) [44]. A prospective study in China pointed out that KIM-1 can be used as an early biomarker for the diagnosis of S-AKI in clinic, and the continuous increase of urinary KIM-1 level may be associated with poor prognosis [45].

L-FABP is expressed in large quantities and binds to excessive free fatty acids, which mediates the apoptosis of tubular epithelial cells through various ways, produces and releases inflammatory factors, and damages the renal tubule interstitium [43]. For in-hospital mortality, the sensitivity and specificity were 93.2% and 78.8%, respectively [46]. Results of a study that included 114 human L-fatty acid-binding protein transgenic mice and 145 septic shock patients diagnosed with acute kidney injury showed that in animal experiments, sepsis can lead to a significant increase in urine L-FABP levels, and urine L-FABP is a more accurate predictor of AKI severity than serum creatinine. Urinary L-FABP measured at admission was significantly higher in non-survivors of septic shock with acute kidney injury at the time of clinical assessment than in survivors. The results also demonstrated that urine L-FABP showed a higher value in the region under the receiver operating characteristics curve when assessing mortality in patients with S-AKI compared to the Acute Physiological and Chronic Health Assessment (APACHE II) and the Assessment of Sepsis Associated Organ Failure (SOFA) scores: L-FABP0.994 [0.956–0.999], APACHEII0.927 [0.873–0.959] and SOFA0.813 [0.733–0.873], $p < 0.05$) [47]. The above results indicate that L-FABP has good value in the diagnosis and prognosis assessment of S-AKI.

Interleukin-18 (IL-18) IL-18 is a 22kDa pro-inflammatory cytokine produced by T cells and macrophages in an unactivated form. After renal ischemia-reperfusion injury (IRI), the level of IL-18 is increased through casPASE proteinase-1 dependence, which is involved in inflammation and immune response [48,49]. IL-18 has been shown to be a sensitive early biomarker of AKI, especially more diagnostic than Scr and urinary NGAL during cardiopulmonary bypass [50]. Clinical studies have found that compared with non-SIAKI patients, S-AKI patients with higher urine IL-18 can predict their clinical renal function deterioration 24 to 48 h in advance [51].

In the study, it was found that cell cycle stasis can help with adequate repair by preventing DNA-damaged cells from dividing. It's a protective mechanism against stress and injury. A test to measure urine [TIMP-2]·[IGFBP7] has received AKI risk stratification regulatory approval in the United States, the European Union and other parts of the world. One study evaluated the ability of urine [TIMP-2]·[IGFBP7] to predict the onset of stage 2 or 3 AKI in 232 patients. Forty (17%) of these patients developed stage 2 or 3 AKI, with an AUC of 0.84 provided by [TIMP-2]·[IGFBP7]. The results show that [TIMP-2]·[IGFBP7] can provide accurate prediction of AKI in patients with sepsis, and the detection performance is not affected by non-renal organ dysfunction [52]. The study also found that TIMP-2 and IGFBP7 outperformed other AKI biomarkers, such as NGAL and KIM-1 ($p < 0.002$) [38]. [TIMP-2]·[IGFBP7] has

also been shown to be a promising biomarker for risk stratification in patients with S-AKI requiring renal replacement therapy [53]. Similarly, a recent analysis of a prospective study involving 433 patients suggests that the combination of [[TIMP-2]·[IGFBP7] and PCT may be a useful tool for identifying and classifying high-risk and short-term adverse outcomes of S-AKI in ICU patients [54].

Cys-C is an ideal endogenous marker of glomerular function. In addition, Cys-C levels were elevated in mild glomerular lesions, independent of diet, inflammation, muscle mass, and tumor, reflecting early changes in glomerular filtration membrane permeability. In order to explore the relationship between Cys-C and S-AKI, Leelahavanichkul et al. [55] found in the mouse model of S-AKI that serum Cys-C began to rise earlier than serum creatinine, indicating that Cys-C may serve as an early biomarker for the occurrence of S-AKI. It was reported that Cys-C in the sepsis group with AKI was significantly higher than that in the non-AKI group, and cystatin C in plasma and urine could well diagnose AKI (AUC was 0.82 and 0.86), which could be used as a good predictor of S-AKI [56]. In addition, a prospective cohort study of 162 patients with sepsis suggests that Cys-C levels in patients with sepsis in ICU may be associated with the development and worsening of AKI [57].

5. Summary

Protective mechanisms in the early stages of SA-AKI allow for some degree of reversal of renal function. However, as the disease progresses, the condition is further exacerbated by mechanisms such as depletion of immune cells, persistent up-regulation of signalling pathways, irreversible damage to endothelial cells. At this stage, the diagnosis and efficacy assessment of sepsis-associated acute kidney injury depends on urine output and creatinine level; however, creatinine level may be affected by high creatine food intake, blood concentration or dilution, delayed elevation due to the disease. Urine output is also influenced by fluid intake to a certain extent, and a series of novel biomarkers of SA-AKI (NGAL, KIM-1, TIMP A series of novel biomarkers for SA-AKI (NGAL, KIM-1, TIMP-2, IGFBP7) have been shown to assist in early Diagnosis and assessment of the condition in clinical practice. Some of these biomarkers can also predict clinical prognosis. Clinical treatment protocols are mainly symptomatic, which may lead to passivity from time to time in the treatment of S-AKI, and potential therapeutic targets for its mechanism of injury remain to be further investigated. In recent years, related biomarkers have become a hot spot in medical research in the aspects of early diagnosis and prognosis monitoring of S-AKI, and their value has been determined. Therefore, it is urgent to conduct large sample prospective studies on reasonable and effective biomarkers to further clarify their diagnostic sensitivity and specificity, so that they can be applied in clinical diagnosis and treatment earlier.

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