Clinical Utility of Interleukins in Sepsis-Associated Acute Kidney Injury: Current Evidence and Future Perspectives

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Sepsis-associated acute kidney injury (SA-AKI) is one of the most frequent and devastating complications of sepsis, substantially increasing morbidity, mortality, length of intensive care unit stay, and long-term risk of chronic kidney disease. Despite advances in supportive care, early diagnosis and accurate risk stratification remain challenging because conventional biomarkers, including serum creatinine and urine output, often fail to detect renal injury during its initial stages. Growing evidence suggests that immune dysregulation plays a central role in the development of SA-AKI, with cytokine imbalance serving as a major driver of endothelial dysfunction, microcirculatory impairment, tubular injury, and multiple organ failure. Among the numerous inflammatory mediators involved, interleukin-6 (IL-6) and interleukin-10 (IL-10) have emerged as two of the most extensively investigated biomarkers due to their complementary roles in regulating the host inflammatory response.

IL-6 is a pleiotropic pro-inflammatory cytokine that rapidly increases during the early phase of sepsis, promoting acute-phase protein synthesis, endothelial activation, leukocyte recruitment, and amplification of systemic inflammation. Elevated circulating IL-6 concentrations consistently correlate with disease severity, septic shock, organ dysfunction, development of SA-AKI, and increased mortality. Conversely, IL-10 functions primarily as an anti-inflammatory cytokine that suppresses excessive immune activation and limits tissue injury. However, sustained elevation of IL-10 reflects immune dysregulation and immunosuppression, predisposing patients to persistent infection, secondary complications, and adverse clinical outcomes. Increasing evidence indicates that simultaneous assessment of IL-6 and IL-10, rather than either biomarker alone, provides a more comprehensive evaluation of the dynamic balance between hyperinflammation and compensatory anti-inflammatory responses throughout the course of sepsis.

This review summarizes the current understanding of the biological functions of IL-6 and IL-10 in the pathogenesis of SA-AKI and critically evaluates their diagnostic, prognostic, and potential therapeutic significance. It further discusses the advantages and limitations of these cytokines as clinical biomarkers, their integration with conventional laboratory parameters and emerging biomarker panels, and their future role in precision medicine. A better understanding of IL-6 and IL-10 biology may facilitate earlier diagnosis, improved prognostic stratification, and the development of individualized therapeutic strategies for patients with sepsis-associated acute kidney injury.

Keywords: Sepsis-associated acute kidney injury; Interleukin-6; Interleukin-10

Introduction

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection and is characterized by progressive organ dysfunction. Despite advances in antimicrobial therapy, hemodynamic support, and intensive care, sepsis continues to impose a major clinical burden because of its high mortality and its association with prolonged hospitalization and long-term disability. The Sepsis-3 definition emphasizes organ dysfunction as the central feature of the syndrome and recommends an acute increase of at least two points in the Sequential Organ Failure Assessment score for its clinical identification. [1]

Acute kidney injury is among the most frequent and serious complications of sepsis. Sepsis-associated acute kidney injury is linked to a higher risk of in-hospital death, prolonged intensive care admission, renal replacement therapy, incomplete renal recovery, chronic kidney disease, and subsequent cardiovascular complications. The association between sepsis and kidney injury is bidirectional, as sepsis may directly initiate renal damage, whereas established acute kidney injury may also increase susceptibility to infection and further systemic deterioration. [2]

The pathophysiology of sepsis-associated acute kidney injury is considerably more complex than the traditional explanation of renal hypoperfusion followed by acute tubular necrosis. Current evidence indicates that renal dysfunction may develop despite preserved or increased global renal blood flow. Endothelial activation, heterogeneous microvascular perfusion, venous congestion, inflammatory signaling, mitochondrial dysfunction, oxidative stress, tubular epithelial adaptation, and altered cellular metabolism all contribute to kidney injury during sepsis. [3]

Immune dysregulation is a central mechanism in this process. Pathogen-associated molecular patterns and damage-associated molecular patterns activate pattern-recognition receptors expressed on circulating immune cells, endothelial cells, and renal tubular epithelial cells. This activation initiates intracellular signaling pathways that promote the release of cytokines, chemokines, reactive oxygen species, and procoagulant mediators, resulting in endothelial barrier disruption, leukocyte recruitment, microvascular thrombosis, and direct tubular injury. [4]

Cytokines are particularly important because they act not only as mediators of tissue injury but also as measurable indicators of the intensity and direction of the host immune response. Their concentrations may change rapidly during sepsis and can reflect the transition from early hyperinflammation to compensatory anti-inflammatory responses and subsequent immune dysfunction. However, their pleiotropic effects, short circulating half-lives, variable release patterns, and dependence on sampling time complicate their interpretation as individual biomarkers. [5]

Interleukin-6 is one of the principal pro-inflammatory cytokines involved in sepsis. It is produced by monocytes, macrophages, endothelial cells, and other tissues following infection or cellular injury. Through classic and trans-signaling pathways, interleukin-6 promotes hepatic acute-phase protein production, leukocyte recruitment, endothelial activation, vascular permeability, coagulation abnormalities, and amplification of systemic inflammation. These effects provide a biological basis for the observed association between elevated interleukin-6 concentrations and the severity of sepsis-related organ dysfunction. [6]

Interleukin-10 is a major anti-inflammatory and immunoregulatory cytokine that limits excessive inflammatory injury by suppressing antigen presentation and reducing the production of pro-inflammatory mediators. Nevertheless, persistent or excessive interleukin-10 elevation may impair antimicrobial immunity, reduce monocyte responsiveness, promote immune paralysis, and increase susceptibility to secondary infection. Thus, interleukin-10 may reflect both an attempt to restore immune homeostasis and the development of clinically important immunosuppression. [7]

The simultaneous evaluation of interleukin-6 and interleukin-10 may therefore provide a more informative representation of sepsis biology than measurement of either cytokine alone. Interleukin-6 predominantly reflects inflammatory activation, whereas interleukin-10 reflects compensatory immune regulation and suppression. Their combined assessment may help characterize the balance between pro-inflammatory and anti-inflammatory responses, identify patients at risk of sepsis-associated acute

kidney injury, and improve prognostic stratification. [8]

Current diagnosis of acute kidney injury continues to depend mainly on changes in serum creatinine and urine output. These parameters have important limitations because serum creatinine rises only after a substantial reduction in glomerular filtration, is influenced by muscle mass and fluid balance, and may be delayed during the early phase of sepsis. Urine output is similarly affected by resuscitation, diuretics, hemodynamic status, and baseline renal function, limiting its ability to distinguish functional changes from established structural kidney injury. [9]

Novel biomarkers, including urinary tissue inhibitor of metalloproteinases-2, insulin-like growth factor-binding protein 7, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and liver-type fatty acid-binding protein, have been investigated for earlier detection of renal stress or tubular injury. Although several have demonstrated promising predictive performance, their availability, cost, variable thresholds, and dependence on clinical context have limited their routine implementation. Cytokines such as interleukin-6 and interleukin-10 may complement these markers by providing information about the systemic immune mechanisms driving renal injury. [10]

Despite increasing interest, the clinical utility of interleukin-6 and interleukin-10 in sepsis-associated acute kidney injury remains uncertain. Available studies differ in patient selection, sepsis definitions, timing of cytokine measurement, assay methods, acute kidney injury criteria, and outcome assessment. Moreover, clear and reproducible cutoff values have not been established, and it remains unclear whether cytokine measurement provides meaningful additional value beyond clinical scores, serum lactate, procalcitonin, serum creatinine, and newer kidney injury biomarkers. [11]

The principal research gap is therefore not the absence of an association between cytokine elevation and adverse outcomes, but the lack of standardized evidence supporting their routine application in clinical decision-making. Future studies must determine whether serial measurements, cytokine trajectories, combined interleukin-6 and interleukin-10 assessment, or integration into multimarker prediction models can improve early diagnosis, distinguish biological subphenotypes, predict renal recovery, and guide individualized therapeutic interventions. [12]

Accordingly, this review examines the biological roles of interleukin-6 and interleukin-10 in sepsis-associated acute kidney injury, evaluates their diagnostic and prognostic performance, discusses their relationship with disease severity and renal outcomes, and identifies the methodological and clinical barriers that must be addressed before their incorporation into routine practice. Particular attention is given to the potential value of combining both cytokines as complementary indicators of inflammatory activation and immune suppression. [13]

Sepsis-Associated Acute Kidney Injury: Clinical Overview

Sepsis-associated acute kidney injury (SA-AKI) is recognized as the most common cause of acute kidney injury in critically ill patients and represents a distinct clinical syndrome resulting from the interaction between systemic infection and a dysregulated host immune response. Unlike other forms of AKI, SA-AKI develops through complex inflammatory, microvascular, metabolic, and cellular mechanisms that extend beyond alterations in renal perfusion alone. Clinically, approximately one-half of patients admitted to intensive care units with sepsis develop AKI, and its occurrence markedly increases the risks of prolonged hospitalization, renal replacement therapy, progression to chronic kidney disease, and both short- and long-term mortality. **[14]**

The diagnosis of SA-AKI remains based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which define AKI by an increase in serum creatinine of ≥0.3 mg/dL within 48 hours, an increase to ≥1.5 times baseline within seven days, or urine output below 0.5 mL/kg/hour for at least six hours. However, establishing the precise onset of SA-AKI is often difficult because sepsis itself influences creatinine production, renal perfusion, fluid balance, and urine output. Aggressive fluid resuscitation may dilute serum creatinine, whereas reduced muscle perfusion decreases creatinine generation, resulting in delayed recognition of kidney injury during the critical early phase of sepsis. **[15]**

The clinical manifestations of SA-AKI range from mild, transient elevations in serum creatinine to severe oliguric renal failure requiring renal replacement therapy. Importantly, recovery is highly

variable. Some patients regain baseline renal function following resolution of sepsis, whereas others progress to persistent kidney dysfunction, chronic kidney disease, or end-stage kidney disease. The likelihood of renal recovery is influenced by the severity and duration of kidney injury, baseline renal function, adequacy of infection control, hemodynamic stability, and persistence of systemic inflammation, emphasizing that SA-AKI is not merely an acute complication but a determinant of long-term renal prognosis. **[16]**

Although serum creatinine and urine output remain the cornerstone of diagnosis, both are functional markers rather than indicators of structural renal injury and frequently fail to detect early tubular damage. Consequently, substantial interest has focused on identifying biomarkers capable of recognizing kidney injury before irreversible functional decline occurs. Novel biomarkers—including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), and urinary tissue inhibitor of metalloproteinases-2/insulin-like growth factor-binding protein-7 ([TIMP-2]·[IGFBP7])—have demonstrated encouraging diagnostic performance. Nevertheless, their clinical implementation remains limited by variability in patient populations, assay availability, cost, and the absence of universally accepted cutoff values. **[17]**

Increasing evidence suggests that inflammatory biomarkers may complement renal injury biomarkers by reflecting the underlying biological processes responsible for kidney damage. Because cytokine activation precedes measurable deterioration in renal function, mediators such as IL-6 and IL-10 have attracted considerable attention as potential tools for early diagnosis, risk stratification, and prognostic assessment. Rather than replacing conventional biomarkers, these cytokines may provide additional insight into the evolving immune response that drives the initiation and progression of SA-AKI, supporting a more individualized approach to patient management. **[18]**

Immunopathogenesis of Sepsis-Associated Acute Kidney Injury

The pathogenesis of sepsis-associated acute kidney injury is multifactorial and reflects a complex interaction between systemic inflammation, immune dysregulation, endothelial injury, microvascular dysfunction, metabolic disturbances, and direct tubular cell damage. Contemporary evidence has shifted the traditional paradigm from renal ischemia alone toward a model in which immune-mediated mechanisms play the dominant role. During sepsis, pathogen-associated molecular patterns (PAMPs) derived from invading microorganisms and damage-associated molecular patterns (DAMPs) released from injured host cells activate pattern-recognition receptors, including Toll-like receptors and NOD-like receptors, expressed on immune cells, endothelial cells, and renal tubular epithelial cells. This activation initiates intracellular signaling cascades that amplify the inflammatory response and contribute to progressive organ dysfunction. **[19]**

Activation of the innate immune system leads to rapid production of numerous pro-inflammatory cytokines, chemokines, and complement mediators that recruit neutrophils, monocytes, and macrophages to sites of infection. Although these responses are essential for pathogen clearance, excessive cytokine production results in widespread endothelial activation, increased vascular permeability, leukocyte adhesion, and dysregulated coagulation. The resulting inflammatory environment promotes renal tubular injury through oxidative stress, mitochondrial dysfunction, apoptosis, and impaired cellular energy metabolism, thereby contributing to the development of AKI even when total renal blood flow is relatively preserved. **[20]**

Endothelial dysfunction represents a pivotal event in SA-AKI. Under physiological conditions, the vascular endothelium maintains microcirculatory homeostasis by regulating vascular tone, leukocyte trafficking, coagulation, and barrier integrity. During sepsis, inflammatory mediators disrupt endothelial glycocalyx structure, increase expression of adhesion molecules, and promote endothelial apoptosis. These changes facilitate leukocyte infiltration, capillary leakage, and interstitial edema while simultaneously activating coagulation pathways that generate microvascular thrombosis. Consequently, oxygen delivery becomes heterogeneous at the tissue level despite apparently adequate systemic hemodynamics, leading to regional hypoxia and progressive renal injury. **[21]**

Microcirculatory alterations further aggravate renal dysfunction by creating areas of capillary shunting

and heterogeneous perfusion throughout the renal cortex and medulla. Inflammatory vasodilation, endothelial swelling, leukocyte plugging, platelet aggregation, and fibrin deposition impair effective oxygen extraction by tubular cells. At the cellular level, excessive production of reactive oxygen species damages mitochondrial respiratory complexes, reduces ATP synthesis, and disrupts ion transport mechanisms required for normal tubular function. Rather than extensive tubular necrosis, many patients exhibit a state of reversible cellular metabolic adaptation characterized by cell-cycle arrest, which may explain the potential for renal recovery if inflammation is promptly controlled. **[22]**

An additional characteristic of sepsis is the simultaneous activation of pro-inflammatory and anti-inflammatory pathways. While early cytokine release initiates host defense, compensatory anti-inflammatory responses develop almost concurrently in an attempt to limit tissue injury. When this balance becomes dysregulated, persistent hyperinflammation may lead to uncontrolled organ damage, whereas excessive anti-inflammatory activity promotes immunosuppression, impaired pathogen clearance, and increased susceptibility to secondary infections. This dynamic immune imbalance forms the biological basis for investigating cytokines such as IL-6 and IL-10 as biomarkers capable of reflecting disease severity, predicting clinical outcomes, and identifying distinct immunological phenotypes among patients with SA-AKI. **[23]**

Cytokine Network in Sepsis and Sepsis-Associated Acute Kidney Injury

Cytokines are low-molecular-weight soluble proteins that regulate communication between immune and non-immune cells during infection and tissue injury. Under physiological conditions, cytokine production is tightly controlled to coordinate pathogen elimination while preserving tissue integrity. During sepsis, however, this regulatory balance becomes profoundly disturbed, resulting in excessive and sustained cytokine release that contributes to widespread inflammation, endothelial dysfunction, coagulation abnormalities, and multiple organ failure. Because cytokines are produced rapidly after activation of innate immunity, they represent some of the earliest measurable indicators of the host response to infection and have therefore become attractive biomarkers for both diagnosis and prognostic assessment. **[24]**

The initial immune response is triggered by recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern-recognition receptors expressed on macrophages, monocytes, dendritic cells, neutrophils, and renal tubular epithelial cells. Activation of these receptors stimulates intracellular signaling pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK), leading to rapid secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8. These mediators amplify inflammation by promoting leukocyte recruitment, endothelial activation, complement activation, and acute-phase protein synthesis, thereby contributing to the systemic manifestations of sepsis. **[25]**

To counterbalance excessive inflammation, anti-inflammatory cytokines are simultaneously released, with IL-10 representing the principal mediator of this compensatory response. IL-10 suppresses macrophage activation, inhibits antigen presentation, reduces synthesis of pro-inflammatory cytokines, and limits tissue injury. Nevertheless, persistent overexpression of IL-10 may impair innate and adaptive immune function, resulting in immune exhaustion, reduced pathogen clearance, and increased susceptibility to secondary infections. Consequently, sepsis is now recognized as a dynamic syndrome characterized by the coexistence of hyperinflammatory and immunosuppressive states rather than a simple progression from one phase to the other. **[26]**

Within this intricate cytokine network, IL-6 and IL-10 occupy central yet complementary positions. IL-6 primarily reflects the magnitude of inflammatory activation and tissue injury, whereas IL-10 mirrors the degree of compensatory immune regulation. Their circulating concentrations often increase simultaneously during severe sepsis, and the relative balance between these cytokines may provide valuable insight into the patient's immunological status. Emerging evidence suggests that combined assessment of IL-6 and IL-10 may better characterize disease severity, predict organ dysfunction, and identify patients at increased risk of developing sepsis-associated acute kidney injury than measurement

of either cytokine alone, supporting their growing role in precision medicine approaches for critically ill patients. **[27]**

Interleukin-6: Biology and Immunological Functions

Interleukin-6 (IL-6) is a multifunctional pleiotropic cytokine that plays a central role in regulating innate and adaptive immune responses, hematopoiesis, and the acute-phase inflammatory reaction. It is produced predominantly by monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, and epithelial cells following stimulation by microbial products, tissue injury, or other pro-inflammatory cytokines. Under physiological conditions, IL-6 contributes to host defense by promoting pathogen clearance and tissue repair. However, excessive or sustained IL-6 production is implicated in numerous inflammatory disorders, including sepsis, autoimmune diseases, cytokine release syndrome, and chronic inflammatory conditions. **[28]**

IL-6 exerts its biological effects through two distinct signaling pathways: classic signaling and trans-signaling. In the classic pathway, IL-6 binds to the membrane-bound IL-6 receptor (IL-6Rα), which is expressed on a limited number of target cells, including hepatocytes and selected leukocyte populations. This complex subsequently associates with glycoprotein 130 (gp130), activating intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3 kinase (PI3K) pathways. Classic signaling is primarily associated with protective, regenerative, and homeostatic immune functions. **[29]**

In contrast, IL-6 trans-signaling occurs when IL-6 binds to a soluble IL-6 receptor (sIL-6R), allowing the cytokine-receptor complex to activate gp130 on nearly all nucleated cells regardless of membrane IL-6 receptor expression. This mechanism substantially broadens the biological activity of IL-6 and is largely responsible for its pro-inflammatory effects. Persistent activation of trans-signaling promotes endothelial dysfunction, increased vascular permeability, leukocyte adhesion, oxidative stress, and sustained inflammatory activation, all of which contribute to tissue injury during severe systemic infections. Selective inhibition of IL-6 trans-signaling has therefore emerged as an attractive therapeutic strategy because it may reduce harmful inflammation while preserving the beneficial physiological functions mediated through classic signaling. **[30]**

IL-6 also serves as a critical link between local immune activation and systemic inflammatory responses. It stimulates hepatocytes to synthesize acute-phase proteins, including C-reactive protein, fibrinogen, and serum amyloid A, while simultaneously promoting fever, lymphocyte differentiation, neutrophil recruitment, and activation of coagulation pathways. During severe infections, circulating IL-6 concentrations may increase several thousand-fold within a short period, making it one of the earliest measurable cytokines released following immune activation. Consequently, IL-6 has become one of the most extensively investigated biomarkers for evaluating inflammatory activity, disease severity, and clinical outcomes in septic patients. **[31]**

Beyond its role as a biomarker, IL-6 actively contributes to the pathogenesis of organ dysfunction through multiple mechanisms. Persistent IL-6 signaling promotes endothelial barrier disruption, microvascular thrombosis, mitochondrial dysfunction, oxidative stress, and tissue edema, thereby aggravating dysfunction of the kidneys, lungs, cardiovascular system, and other organs during sepsis. These biological properties explain the consistent association between elevated IL-6 concentrations and adverse clinical outcomes and provide the rationale for exploring IL-6-targeted therapies as part of future precision medicine strategies in critically ill patients. **[32]**

Clinical Utility of Interleukin-6 in Sepsis-Associated Acute Kidney Injury

IL-6 has emerged as one of the earliest and most extensively investigated inflammatory biomarkers in sepsis because of its rapid release following activation of innate immunity. Plasma IL-6 concentrations increase within a few hours after exposure to infectious stimuli, preceding the elevation of conventional inflammatory markers such as C-reactive protein (CRP). This early kinetic profile enables IL-6 to reflect the intensity of the host inflammatory response before overt clinical deterioration occurs, making it a promising biomarker for the early identification of patients at risk of developing severe sepsis and sepsis-associated acute kidney injury (SA-AKI). **[33]**

Several clinical studies have demonstrated that circulating IL-6 concentrations correlate closely with disease severity, Sequential Organ Failure Assessment (SOFA) scores, development of septic shock, and mortality. Patients with persistently elevated IL-6 levels generally exhibit more pronounced systemic inflammation, greater endothelial dysfunction, and a higher incidence of multiple organ failure than those whose cytokine concentrations decline during treatment. Dynamic monitoring of IL-6 therefore appears to provide greater prognostic value than a single measurement, as persistent elevation may indicate ongoing immune activation and inadequate control of the underlying infectious process. **[34]**

Within the kidney, IL-6 contributes directly to the pathogenesis of SA-AKI through several complementary mechanisms. Excessive IL-6 signaling promotes endothelial activation, increased vascular permeability, leukocyte infiltration, oxidative stress, mitochondrial dysfunction, and tubular epithelial cell injury. In addition, IL-6 amplifies coagulation activation and microvascular dysfunction, resulting in heterogeneous renal perfusion despite preserved global renal blood flow. Consequently, elevated circulating IL-6 reflects not only systemic inflammation but also biological processes that directly participate in renal injury and dysfunction during sepsis. **[35]**

The prognostic significance of IL-6 extends beyond the development of AKI. Higher plasma IL-6 concentrations have consistently been associated with increased requirements for vasopressor support, prolonged intensive care unit stay, need for renal replacement therapy, and higher short-term mortality. Moreover, serial measurements appear to outperform isolated baseline values because declining IL-6 levels during treatment generally indicate resolution of inflammation, whereas persistently elevated concentrations identify patients with continued immune dysregulation and poor clinical outcomes. These findings support the incorporation of IL-6 into multimarker prognostic models rather than its use as an isolated predictor. **[36]**

Despite its promising clinical utility, IL-6 has important limitations that restrict its use as a standalone biomarker. Elevated IL-6 concentrations are observed in numerous inflammatory conditions, including autoimmune diseases, major trauma, burns, surgery, and malignancy, thereby limiting its specificity for sepsis. Furthermore, differences in assay methodology, sampling time, patient populations, and proposed cutoff values contribute to variability among published studies. Consequently, current evidence suggests that IL-6 should be interpreted alongside clinical assessment, severity scores, and complementary biomarkers such as procalcitonin, C-reactive protein, and IL-10 to maximize diagnostic and prognostic accuracy in patients with SA-AKI. **[37]**

Interleukin-10: Biology and Immunological Functions

Interleukin-10 (IL-10) is a potent anti-inflammatory and immunoregulatory cytokine that plays a fundamental role in maintaining immune homeostasis during infection. It is primarily produced by monocytes, macrophages, dendritic cells, regulatory T lymphocytes, T helper cells, and regulatory B cells following activation of innate and adaptive immune responses. Unlike pro-inflammatory cytokines that amplify host defense mechanisms, IL-10 functions principally to limit excessive inflammation, thereby protecting tissues from immune-mediated injury. However, persistent or excessive IL-10 production may impair pathogen clearance and contribute to the immunosuppressive state characteristic of advanced sepsis. **[38]**

The biological effects of IL-10 are mediated through binding to a heterotetrameric receptor complex composed of IL-10 receptor alpha (IL-10RA) and IL-10 receptor beta (IL-10RB) subunits. Ligand binding activates the Janus kinase (JAK1) and tyrosine kinase 2 (TYK2) signaling pathways, leading predominantly to phosphorylation of signal transducer and activator of transcription-3 (STAT3). Activated STAT3 subsequently induces transcription of anti-inflammatory genes while suppressing nuclear factor-κB (NF-κB) activation and the expression of multiple pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-12. This signaling pathway enables IL-10 to serve as one of the most important endogenous regulators of inflammatory responses. **[39]**

IL-10 exerts broad immunomodulatory effects on both innate and adaptive immunity. It inhibits macrophage and dendritic cell activation, reduces antigen presentation by decreasing major

histocompatibility complex class II expression, suppresses production of inflammatory cytokines and chemokines, and limits T-cell activation and proliferation. Conversely, IL-10 promotes B-cell survival, differentiation, and antibody production while supporting regulatory T-cell function, thereby contributing to restoration of immune homeostasis after pathogen elimination. These diverse biological activities illustrate the pleiotropic nature of IL-10 and explain its dual protective and potentially detrimental roles during sepsis. **[40]**

In sepsis, IL-10 production increases rapidly as part of the compensatory anti-inflammatory response that accompanies systemic inflammation. Initially, this response protects against excessive cytokine-mediated tissue injury; however, sustained elevation of IL-10 may result in immune paralysis characterized by reduced monocyte HLA-DR expression, impaired cytokine production, diminished phagocytic activity, and increased susceptibility to secondary infections. Consequently, persistently elevated IL-10 concentrations often reflect profound immune dysfunction rather than successful resolution of inflammation, making IL-10 an important indicator of disease progression and adverse clinical outcomes. **[41]**

The dual biological functions of IL-10 have attracted considerable interest regarding its potential therapeutic implications. While augmentation of IL-10 activity may reduce inflammatory tissue damage during the early hyperinflammatory phase of sepsis, excessive immunosuppression remains a major concern. Conversely, strategies aimed at reversing prolonged IL-10-mediated immune paralysis may enhance antimicrobial immunity during later stages of sepsis. These observations underscore the importance of understanding the temporal dynamics of IL-10 expression and support its emerging role as both a biomarker of immune status and a potential target for individualized immunomodulatory therapy. **[42]**

Clinical Utility of Interleukin-10 in Sepsis-Associated Acute Kidney Injury

Compared with IL-6, IL-10 is regarded primarily as a prognostic rather than a diagnostic biomarker in sepsis. Although circulating IL-10 concentrations increase early during infection, their greatest clinical significance lies in reflecting the magnitude of the compensatory anti-inflammatory response syndrome (CARS) that develops alongside systemic inflammation. Elevated IL-10 concentrations indicate activation of endogenous mechanisms aimed at limiting inflammatory tissue injury; however, persistent overproduction often signifies profound immune dysregulation and is consistently associated with poor clinical outcomes in critically ill patients. **[43]**

Several clinical investigations have demonstrated that patients with severe sepsis, septic shock, and sepsis-associated acute kidney injury exhibit significantly higher IL-10 concentrations than patients with uncomplicated infection. Furthermore, persistently elevated IL-10 levels correlate with higher Sequential Organ Failure Assessment (SOFA) scores, increased vasopressor requirements, prolonged intensive care unit stay, greater incidence of multiple organ dysfunction syndrome, and higher short-term mortality. These findings suggest that IL-10 reflects the severity of immune dysfunction rather than infection alone, making it a valuable biomarker for risk stratification. **[44]**

Experimental and clinical evidence also supports a direct relationship between IL-10 and renal injury during sepsis. Excessive inflammatory activation within the kidney stimulates compensatory IL-10 production, which initially limits tubular inflammation and reduces cytokine-mediated cellular damage. Nevertheless, sustained IL-10 elevation may suppress macrophage and lymphocyte function, impair bacterial clearance, and prolong systemic inflammation, thereby indirectly contributing to persistent renal dysfunction. Consequently, IL-10 should be interpreted as a dynamic marker reflecting the evolving balance between protective immune regulation and harmful immunosuppression rather than as a simple indicator of anti-inflammatory activity. **[45]**

Recent studies have further highlighted the prognostic importance of IL-10 in predicting the development and progression of sepsis-induced acute kidney injury. Elevated serum IL-10 concentrations have been associated with an increased likelihood of AKI, poorer renal recovery, and higher mortality among critically ill patients. Moreover, genetic and biochemical analyses suggest that IL-10 may serve as an independent predictor of SA-AKI when combined with established clinical

variables, supporting its potential incorporation into multimarker prediction models for early risk assessment. **[46]**

Despite these promising observations, several limitations currently restrict the routine clinical application of IL-10. Considerable variability exists regarding assay techniques, timing of blood sampling, proposed diagnostic thresholds, and patient populations, making direct comparison between studies difficult. In addition, elevated IL-10 concentrations are not unique to sepsis and may occur in autoimmune diseases, chronic inflammatory disorders, malignancies, and viral infections. Consequently, current evidence supports the use of IL-10 as part of an integrated biomarker strategy, particularly when interpreted alongside IL-6, conventional inflammatory markers, and validated clinical severity scores, rather than as a standalone prognostic indicator. **[47]**

Combined Clinical Value of Interleukin-6 and Interleukin-10 in Sepsis-Associated Acute Kidney Injury

Although IL-6 and IL-10 individually provide valuable clinical information, increasing evidence indicates that their combined assessment more accurately reflects the complex immune response observed during sepsis. IL-6 predominantly represents the magnitude of the pro-inflammatory response, whereas IL-10 reflects activation of compensatory anti-inflammatory mechanisms. Simultaneous measurement of both cytokines therefore provides a more comprehensive evaluation of the balance between hyperinflammation and immunosuppression, two biological processes that coexist throughout the course of sepsis and collectively influence the development of organ dysfunction, including sepsis-associated acute kidney injury (SA-AKI). **[48]**

Several studies have demonstrated that patients with persistently elevated concentrations of both IL-6 and IL-10 experience significantly worse clinical outcomes than those with isolated elevation of either cytokine. Concurrent increases in these biomarkers have been associated with more severe organ dysfunction, higher Sequential Organ Failure Assessment (SOFA) scores, increased incidence of septic shock, prolonged intensive care unit stay, greater need for renal replacement therapy, and increased mortality. These findings suggest that simultaneous activation of inflammatory and anti-inflammatory pathways reflects profound immune dysregulation and identifies a subgroup of patients at particularly high risk of adverse outcomes. **[49]**

Beyond absolute cytokine concentrations, the dynamic relationship between IL-6 and IL-10 may provide additional prognostic information. Changes in their concentrations over time may better represent the evolution of the host immune response than single baseline measurements. Patients demonstrating sustained elevation of both cytokines despite appropriate antimicrobial therapy and supportive care generally exhibit persistent immune dysfunction and poorer prognosis, whereas declining cytokine levels often parallel clinical improvement and recovery of organ function. Consequently, serial cytokine monitoring may have greater clinical utility than isolated measurements obtained at hospital admission. **[50]**

Current evidence therefore supports the concept that IL-6 and IL-10 should be considered complementary rather than competing biomarkers. Their combined interpretation, together with established clinical scores and conventional laboratory markers, has the potential to improve early risk stratification, identify distinct immunological phenotypes, and facilitate personalized management strategies in patients with SA-AKI. Nevertheless, before routine implementation can be recommended, large prospective multicenter studies are needed to establish standardized sampling protocols, validate clinically relevant cutoff values, and determine whether cytokine-guided therapeutic approaches improve patient outcomes.

Conclusion

Sepsis-associated acute kidney injury remains a major cause of morbidity and mortality in critically ill patients and reflects the complex interaction between systemic inflammation, immune dysregulation, endothelial dysfunction, and renal cellular injury. Among the numerous inflammatory mediators involved, interleukin-6 and interleukin-10 have emerged as complementary biomarkers that provide valuable insight into the host immune response. IL-6 reflects the magnitude of early pro-inflammatory

activation and correlates with disease severity, organ dysfunction, and mortality, whereas IL-10 primarily indicates compensatory anti-inflammatory responses and immune suppression associated with adverse outcomes. Current evidence suggests that the combined assessment of both cytokines offers greater diagnostic and prognostic value than either biomarker alone and may improve early risk stratification when integrated with conventional clinical and laboratory parameters. However, variability in assay methods, sampling time, and cutoff values currently limits their routine clinical application. Future large-scale prospective studies are required to standardize their use, validate multimarker strategies, and determine whether cytokine-guided management can facilitate precision medicine and improve outcomes in patients with sepsis-associated acute kidney injury.

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