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Biomarkers of Sepsis-Associated Acute Kidney Injury: From Conventional Indicators to Emerging Precision Medicine

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ABSTRACT

Background: Sepsis-associated acute kidney injury (SA-AKI) is one of the most frequent and devastating complications of sepsis, contributing substantially to intensive care unit admissions, prolonged hospitalization, chronic kidney disease, and mortality. Early diagnosis remains challenging because conventional indicators, including serum creatinine and urine output, often reflect renal dysfunction only after significant kidney injury has already occurred. This diagnostic delay limits opportunities for timely intervention and highlights the need for more sensitive and specific biomarkers capable of identifying kidney injury at an earlier stage.

Aim: This review aims to summarize the current evidence regarding biomarkers used in the diagnosis and prognosis of SA-AKI, ranging from conventional renal function indicators to emerging molecular and immune biomarkers. It also explores recent advances in precision medicine, including multi-biomarker panels, omics technologies, and artificial intelligence-based predictive models, with an emphasis on their potential to improve early detection, risk stratification, prognostic assessment, and individualized patient management.

Conclusion: Conventional biomarkers remain indispensable in routine clinical practice but possess important limitations in sensitivity and specificity for the early detection of SA-AKI. Emerging biomarkers—including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C, tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), interleukins, endothelial injury markers, and novel omics-derived candidates—have demonstrated promising diagnostic and prognostic value. Integrating these biomarkers into multimarker strategies, supported by machine learning and precision medicine approaches, may substantially enhance clinical decision-making and facilitate personalized therapeutic interventions. Nevertheless, large multicenter validation studies, standardized assay protocols, and cost-effectiveness analyses are still required before widespread implementation in routine clinical practice. Future biomarker-guided precision medicine strategies have the potential to transform the management of SA-AKI by enabling earlier diagnosis, more accurate prognostication, and targeted therapeutic approaches that ultimately improve patient outcomes.

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Keywords: Sepsis-associated acute kidney injury; Biomarkers; Precision medicine

1. Introduction

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection and remains a major cause of organ dysfunction, intensive care unit admission, and mortality worldwide. Among its complications, sepsis-associated acute kidney injury (SA-AKI) is particularly important because it occurs frequently in critically ill patients and is associated with prolonged hospitalization, renal replacement therapy, incomplete renal recovery, chronic kidney disease, and increased short- and long-term mortality. SA-AKI should therefore be regarded as a distinct clinical phenotype of acute kidney injury rather than a simple consequence of systemic hypotension or reduced renal perfusion. [1]

The pathophysiology of SA-AKI is complex and involves interactions among systemic and intrarenal inflammation, endothelial dysfunction, microcirculatory abnormalities, oxidative stress, mitochondrial injury, coagulation disturbances, and tubular epithelial cell dysfunction. Contemporary evidence indicates that global renal blood flow may be preserved or even increased in some patients despite the development of AKI, challenging the traditional concept that renal ischemia and acute tubular necrosis are the sole mechanisms responsible for kidney dysfunction during sepsis. This evolving understanding has increased interest in biomarkers that reflect specific biological processes rather than functional impairment alone. [2]

Current diagnosis and staging of SA-AKI rely mainly on changes in serum creatinine and urine output according to established acute kidney injury criteria. However, both indicators have substantial limitations. Serum creatinine may rise only after a considerable reduction in glomerular filtration, is affected by muscle mass and fluid accumulation, and may be diluted during aggressive resuscitation. Urine output is influenced by hemodynamic status, diuretic use, fluid administration, and pre-existing kidney function. These limitations can delay recognition of renal injury and reduce the opportunity for timely preventive or supportive interventions. [3]

The search for earlier and more biologically informative markers has led to the investigation of tubular injury biomarkers, including neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and liver-type fatty acid-binding protein; cell-cycle arrest biomarkers, particularly tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7; and functional biomarkers such as cystatin C. Inflammatory cytokines, endothelial injury markers, immune mediators, extracellular vesicles, and omics-derived signatures are also being explored because they may identify renal stress or tissue injury before conventional measures become abnormal. [4]

Despite encouraging findings, the clinical performance of emerging biomarkers varies according to the timing of measurement, biological specimen, assay platform, sepsis severity, baseline renal function, and selected clinical outcome. No single biomarker captures the full biological heterogeneity of SA-AKI, and many markers cannot reliably distinguish kidney injury caused directly by sepsis from renal dysfunction related to nephrotoxic medications, venous congestion, mechanical ventilation, or other critical illness-associated factors. Consequently, multimarker strategies integrating functional, structural, inflammatory, and endothelial indicators may provide greater diagnostic and prognostic accuracy than isolated biomarker measurements. [5]

Precision medicine offers a framework for integrating biomarker profiles with clinical characteristics, severity scores, temporal trajectories, and computational prediction models. Such an approach may facilitate earlier recognition of high-risk patients, differentiation of biological subphenotypes, prediction of renal replacement therapy requirements, assessment of renal recovery, and selection of individualized therapeutic strategies. However, widespread implementation requires standardized assays, reproducible cutoff values, external validation in diverse populations, and evidence that biomarker-guided decisions improve clinically meaningful outcomes. [6]

Accordingly, this review aims to examine conventional and emerging biomarkers of SA-AKI, evaluate their biological basis and clinical performance, and discuss their potential roles in early diagnosis, prognosis, monitoring, and therapeutic stratification. Particular emphasis is placed on the transition from isolated indicators of renal dysfunction toward integrated multimarker and precision medicine approaches capable of addressing the biological heterogeneity of sepsis-associated kidney injury. [7]

Clinical and Pathophysiological Context of Sepsis-Associated Acute Kidney Injury

Sepsis-associated acute kidney injury is a heterogeneous syndrome that may develop at any stage of sepsis and varies from mild, transient functional impairment to severe kidney failure requiring renal replacement therapy. Its incidence increases with the severity of infection, the presence of septic shock, pre-existing chronic kidney disease, advanced age, diabetes, cardiovascular

disease, exposure to nephrotoxic medications, and the requirement for mechanical ventilation or vasopressor support. The occurrence of SA-AKI is consistently associated with longer intensive care unit and hospital stays, increased treatment costs, reduced likelihood of complete renal recovery, and substantially higher mortality than sepsis without kidney injury. [8]

The relationship between sepsis and AKI is bidirectional. Sepsis may induce kidney injury through systemic and intrarenal inflammation, microvascular dysfunction, endothelial activation, altered renal perfusion, oxidative stress, and tubular epithelial injury. Conversely, established AKI can impair innate and adaptive immune responses, alter cytokine clearance, disrupt distant-organ communication, and increase susceptibility to secondary infection. This reciprocal interaction may create a self-perpetuating cycle in which renal dysfunction intensifies systemic inflammation and sepsis severity, complicating both diagnosis and treatment. [9]

Traditional explanations attributed SA-AKI predominantly to systemic hypotension, reduced renal blood flow, and ischemic acute tubular necrosis. Current evidence indicates that this model is incomplete because renal dysfunction may occur despite preserved or increased total renal blood flow. Instead, heterogeneous cortical and medullary perfusion, intrarenal shunting, venous congestion, endothelial leakage, glycocalyx degradation, leukocyte adhesion, and microthrombus formation can impair local oxygen delivery and utilization. These alterations help explain why systemic hemodynamic normalization does not always result in immediate renal recovery. [10]

Inflammatory activation is central to SA-AKI pathogenesis. Pathogen-associated molecular patterns and damage-associated molecular patterns bind to pattern-recognition receptors on circulating leukocytes, endothelial cells, and renal tubular epithelial cells, triggering the release of cytokines, chemokines, reactive oxygen species, and coagulation mediators. Excessive activation of these pathways disrupts endothelial barrier integrity, promotes interstitial edema, recruits inflammatory cells, and contributes to mitochondrial dysfunction and tubular cell-cycle arrest. These molecular events may begin before measurable changes in serum creatinine or urine output appear. [11]

Renal tubular epithelial cells are active participants rather than passive victims in SA-AKI. In response to inflammatory and metabolic stress, these cells can alter gene expression, reduce energy-consuming transport functions, enter cell-cycle arrest, and release injury-associated proteins into the blood or urine. Although these adaptive responses may initially preserve cell survival, persistent stress can lead to apoptosis, necroptosis, pyroptosis, ferroptosis, and maladaptive repair. Biomarkers released during these processes may therefore provide earlier and more mechanistically specific information than conventional measures of glomerular filtration. [12]

The clinical course of SA-AKI is highly variable. Some patients experience rapid reversal after infection control and hemodynamic stabilization, whereas others develop persistent AKI, acute kidney disease, or chronic kidney disease. The severity and duration of kidney injury, baseline renal reserve, cumulative fluid balance, repeated septic insults, and requirement for renal replacement therapy all influence long-term outcomes. Biomarkers capable of distinguishing transient functional changes from structural injury may therefore assist clinicians in predicting renal recovery and identifying patients who require closer follow-up after hospital discharge. [13]

This biological and clinical heterogeneity creates major challenges for biomarker development. A useful SA-AKI biomarker should ideally detect kidney stress before irreversible injury, distinguish structural damage from functional decline, identify the predominant pathophysiological mechanism, provide prognostic information, respond dynamically to clinical improvement or deterioration, and add meaningful value beyond established clinical scores. These requirements explain why a single universal marker is unlikely to be sufficient and why integrated biomarker panels are increasingly being investigated. [14]

Characteristics of an Ideal Biomarker in Sepsis-Associated Acute Kidney Injury

The search for reliable biomarkers in sepsis-associated acute kidney injury (SA-AKI) has been driven by the limitations of conventional diagnostic tools and the complex biological mechanisms underlying renal injury during sepsis. An ideal biomarker should accurately reflect the presence of kidney stress or injury before clinically significant loss of renal function occurs. Early identification is particularly important because therapeutic interventions are most effective before irreversible tubular damage develops. Therefore, biomarkers capable of detecting subclinical kidney injury have the potential to improve clinical outcomes by facilitating prompt diagnosis, early optimization of hemodynamics, avoidance of nephrotoxic agents, and timely implementation of kidney-protective strategies. [15]

In addition to early detection, an ideal biomarker should possess high diagnostic accuracy, with excellent sensitivity and specificity for distinguishing SA-AKI from other causes of renal dysfunction encountered in critically ill patients. Since serum creatinine may increase in response to numerous non-renal factors and urine output is influenced by fluid status, vasopressor therapy, and diuretic administration, novel biomarkers should provide greater biological specificity by directly reflecting structural kidney injury, tubular stress, endothelial dysfunction, inflammation, or cellular damage. This distinction is essential because functional decline and structural injury do not always occur simultaneously during sepsis. [16]

A clinically useful biomarker should also provide prognostic information beyond diagnosis alone. Ideally, it should identify patients at high risk for persistent kidney injury, renal replacement therapy, multiple organ dysfunction, prolonged intensive care unit stay, progression to chronic kidney disease, and mortality. Dynamic changes in biomarker concentrations during hospitalization may further assist clinicians in monitoring disease progression, evaluating response to treatment, and predicting renal recovery. Such prognostic capability would support individualized clinical decision-making and optimize resource allocation in critically ill patients. [17]

Another important characteristic is biological plausibility. Biomarkers should reflect specific mechanisms involved in the pathogenesis of SA-AKI, including tubular epithelial injury, inflammatory activation, oxidative stress, endothelial dysfunction, microvascular injury, mitochondrial damage, or cell-cycle arrest. Mechanistically relevant biomarkers not only improve understanding of disease biology but may also facilitate patient stratification according to underlying pathological pathways, thereby supporting the development of targeted therapeutic interventions within a precision medicine framework. [18]

Practical considerations are equally important for successful clinical implementation. An ideal biomarker should be measurable using standardized, rapid, reproducible, and cost-effective laboratory assays with minimal interobserver variability. Results should be available within a clinically relevant timeframe to influence therapeutic decisions, particularly during the early hours of sepsis management. Furthermore, validated cutoff values should remain consistent across different patient populations, healthcare settings, and laboratory platforms to facilitate widespread adoption into routine clinical practice. [19]

Despite substantial advances in biomarker research, no single biomarker currently fulfills all these criteria. Individual biomarkers often reflect only one aspect of the complex pathophysiology of SA-AKI and may be influenced by underlying chronic kidney disease, systemic inflammation, comorbid illnesses, or the timing of sample collection. Consequently, increasing evidence supports the use of multimarker panels that combine functional, structural, inflammatory, and endothelial biomarkers with clinical variables and machine learning algorithms to improve diagnostic accuracy, prognostic performance, and personalized management of patients with SA-AKI. [20]

Conventional Biomarkers of Sepsis-Associated Acute Kidney Injury

Serum Creatinine

Serum creatinine remains the cornerstone biomarker for diagnosing and staging acute kidney injury and is incorporated into the Kidney Disease: Improving Global Outcomes (KDIGO) diagnostic criteria. It is an inexpensive, widely available, and standardized laboratory test that reflects changes in glomerular filtration rate (GFR). However, in patients with sepsis-associated acute kidney injury (SA-AKI), serum creatinine has several important limitations. Its concentration often increases only after approximately 50% of renal function has already been lost, resulting in delayed diagnosis during the early phase of kidney injury when therapeutic interventions may be most effective. Moreover, serum creatinine is influenced by multiple non-renal factors, including age, sex, muscle mass, nutritional status, liver dysfunction, fluid overload, and medications, all of which are frequently altered in critically ill septic patients. Consequently, serum creatinine reflects functional impairment rather than direct structural kidney injury and lacks sufficient sensitivity for the early detection of SA-AKI. Despite these shortcomings, it continues to serve as the clinical reference standard against which emerging biomarkers are evaluated because of its universal availability and established role in current diagnostic guidelines. [21]

Urine Output

Urine output is another essential component of the KDIGO criteria and provides a simple bedside assessment of renal function. Oliguria often represents one of the earliest clinical manifestations of acute kidney injury and may precede detectable increases in serum creatinine. Continuous urine output monitoring allows clinicians to identify deteriorating renal function rapidly, particularly in critically ill patients receiving intensive monitoring. Nevertheless, urine output has limited specificity because it

is affected by numerous physiological and therapeutic factors, including intravascular volume status, cardiac output, vasopressor administration, diuretic therapy, mechanical ventilation, and pre-existing chronic kidney disease. In septic patients undergoing aggressive fluid resuscitation, preserved urine output does not necessarily exclude structural renal injury, whereas transient oliguria may occur without permanent kidney damage. Therefore, urine output should always be interpreted within the broader clinical context and in combination with other laboratory and clinical findings rather than as an isolated diagnostic indicator. [22]

Blood Urea Nitrogen

Blood urea nitrogen (BUN) is another traditional marker used to assess renal function in critically ill patients. Urea is synthesized in the liver through protein metabolism and excreted primarily by glomerular filtration with partial tubular reabsorption. Elevated BUN levels may indicate impaired renal excretory function but are considerably less specific than serum creatinine because they are influenced by numerous non-renal factors, including gastrointestinal bleeding, high-protein intake, catabolic state, corticosteroid therapy, dehydration, and hepatic function. In sepsis, increased protein catabolism and altered hepatic metabolism frequently contribute to elevated BUN independently of kidney injury, thereby reducing its diagnostic accuracy for SA-AKI. Although BUN alone has limited value for early diagnosis, it remains useful when interpreted alongside serum creatinine, urine output, and the overall clinical picture, particularly in evaluating volume status and monitoring disease progression. [23]

Limitations of Conventional Biomarkers

Although serum creatinine, urine output, and BUN remain indispensable components of routine clinical assessment, they primarily reflect established functional impairment rather than the underlying biological processes responsible for kidney injury. None of these conventional biomarkers can reliably distinguish transient functional changes from structural tubular damage, predict renal recovery, identify patients at highest risk before overt AKI develops, or provide mechanistic insight into inflammatory or endothelial injury. Their diagnostic performance is further compromised by the profound physiological alterations that accompany sepsis, including fluid shifts, systemic inflammation, altered muscle metabolism, and hemodynamic instability. These limitations have stimulated intensive research into novel biomarkers capable of detecting renal stress, tubular injury, endothelial dysfunction, and immune activation at much earlier stages of disease, thereby supporting precision medicine approaches for patients with SA-AKI. [24]

Tubular Injury Biomarkers

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the earliest and most extensively investigated biomarkers of tubular injury in acute kidney injury. It is a 25-kDa glycoprotein belonging to the lipocalin family and is produced by neutrophils and renal tubular epithelial cells following ischemic or inflammatory injury. In SA-AKI, NGAL expression increases rapidly in response to inflammatory cytokines, oxidative stress, and direct tubular damage, with detectable elevations in both plasma and urine occurring within 2–6 hours after renal insult, substantially earlier than serum creatinine. Numerous clinical studies have demonstrated that NGAL has good diagnostic performance for the early detection of SA-AKI and is associated with disease severity, need for renal replacement therapy, and mortality. However, because NGAL is also released during systemic inflammation, bacterial infection, trauma, and chronic kidney disease, elevated concentrations may not always reflect isolated renal injury, limiting its specificity in septic patients. [25]

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein that is minimally expressed in healthy kidneys but becomes markedly upregulated in proximal tubular epithelial cells following ischemic or toxic injury. After tubular damage, the extracellular domain of KIM-1 is cleaved and released into the urine, making urinary KIM-1 a sensitive indicator of structural tubular injury. In patients with SA-AKI, increased urinary KIM-1 concentrations correlate with the severity of tubular damage and may predict progression to severe AKI and adverse clinical outcomes. Unlike serum creatinine, which reflects reduced filtration, KIM-1 directly represents epithelial cell injury and therefore provides complementary information regarding renal pathology. Nevertheless, KIM-1 concentrations may also increase in chronic kidney disease and other forms of tubular injury, necessitating careful interpretation within the clinical context. [26]

Liver-Type Fatty Acid-Binding Protein (L-FABP)

Liver-type fatty acid-binding protein (L-FABP) is a small intracellular protein expressed predominantly in the proximal renal tubules, where it participates in intracellular lipid transport and protects cells from oxidative stress. During ischemia, hypoxia, or inflammatory injury, L-FABP is released into the urine as a consequence of tubular epithelial damage. In SA-AKI, urinary L-FABP concentrations increase early during renal injury and have been associated with disease severity, progression to advanced AKI stages, and short-term mortality. Because oxidative stress is a major contributor to septic renal injury, L-FABP provides mechanistic insight into one of the principal pathways involved in SA-AKI pathogenesis. Several studies suggest that combining L-FABP with other tubular injury biomarkers improves diagnostic accuracy compared with individual biomarker measurement alone. [27]

N-Acetyl-β-D-Glucosaminidase (NAG)

N-Acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme abundantly present within proximal tubular epithelial cells. Owing to its relatively large molecular weight, NAG is not filtered through the glomerulus under normal physiological conditions. Increased urinary NAG therefore reflects tubular epithelial cell injury and lysosomal disruption rather than impaired glomerular filtration. Elevated urinary NAG has been reported in patients with SA-AKI and correlates with tubular damage and worsening renal function. However, NAG lacks disease specificity because increased urinary concentrations may also occur in diabetic nephropathy, chronic kidney disease, drug-induced nephrotoxicity, and other renal disorders. Consequently, although NAG contributes valuable information regarding tubular integrity, its role is generally complementary rather than diagnostic when used independently. [28]

Clinical Significance of Tubular Injury Biomarkers

Collectively, tubular injury biomarkers provide important advantages over conventional renal function tests by detecting structural kidney injury before measurable declines in glomerular filtration occur. Unlike serum creatinine and urine output, these biomarkers reflect specific cellular responses to ischemia, inflammation, oxidative stress, and epithelial damage, allowing earlier recognition of SA-AKI and more accurate risk stratification. Nevertheless, individual biomarkers vary in sensitivity, specificity, biological half-life, and susceptibility to systemic inflammation. Current evidence therefore supports integrating multiple tubular injury biomarkers with functional markers and clinical variables to improve diagnostic precision and facilitate earlier therapeutic intervention within precision medicine strategies for SA-AKI. [29]

Cell-Cycle Arrest Biomarkers

Tissue Inhibitor of Metalloproteinases-2 (TIMP-2)

Tissue inhibitor of metalloproteinases-2 (TIMP-2) is a stress-responsive protein released predominantly by renal tubular epithelial cells following exposure to inflammatory, ischemic, or toxic insults. Rather than indicating irreversible cell death, TIMP-2 reflects early cellular stress that induces G1 cell-cycle arrest, a protective mechanism allowing damaged tubular cells to repair DNA and restore normal cellular function before proliferation. In sepsis-associated acute kidney injury (SA-AKI), urinary TIMP-2 concentrations increase several hours before detectable changes in serum creatinine or urine output, making it one of the earliest indicators of impending kidney injury. Elevated urinary TIMP-2 has consistently been associated with increased risk of moderate-to-severe AKI, prolonged intensive care unit stay, renal replacement therapy, and mortality. Because it reflects an adaptive stress response rather than established structural damage, TIMP-2 is particularly valuable for identifying patients at risk before irreversible renal injury develops. [30]

Insulin-Like Growth Factor-Binding Protein 7 (IGFBP7)

Insulin-like growth factor-binding protein 7 (IGFBP7) is another key mediator of cell-cycle arrest that complements the biological activity of TIMP-2. Following exposure to inflammatory cytokines, oxidative stress, mitochondrial dysfunction, or hypoxia, renal tubular epithelial cells release IGFBP7, which promotes transient arrest of the G1 phase of the cell cycle by regulating cyclin-dependent kinase pathways. This adaptive response limits cellular proliferation under unfavorable conditions and preserves genomic integrity while allowing recovery from injury. Similar to TIMP-2, urinary IGFBP7 concentrations increase early during SA-AKI and correlate with disease severity and adverse clinical outcomes. Experimental studies also suggest that IGFBP7 participates in inflammatory signaling and apoptosis, highlighting its role as both a biomarker and a potential mediator of kidney injury progression. [31]

Combined TIMP-2 × IGFBP7 (NephroCheck®)

The product of urinary TIMP-2 and IGFBP7 concentrations, expressed as [TIMP-2]·[IGFBP7], represents the first biomarker panel approved for clinical assessment of AKI risk. Commercially available as the NephroCheck® test, this assay identifies patients at increased risk of developing moderate-to-severe AKI within the subsequent 12–24 hours. Numerous clinical studies have demonstrated that the combined biomarker performs better than either TIMP-2 or IGFBP7 alone because it reflects complementary mechanisms of tubular stress and cell-cycle arrest. In critically ill patients with sepsis, elevated [TIMP-2]·[IGFBP7] values have shown good predictive accuracy for AKI development, renal non-recovery, need for renal replacement therapy, and short-term mortality. Importantly, these biomarkers identify renal stress before overt functional decline, thereby providing an opportunity for preventive interventions such as optimization of hemodynamics, avoidance of nephrotoxins, and implementation of kidney-protective care bundles. [32]

Clinical Utility and Current Limitations

Cell-cycle arrest biomarkers represent a major advance in the early diagnosis of SA-AKI because they identify reversible cellular stress before permanent tubular damage occurs. Their incorporation into clinical practice may facilitate risk stratification, individualized monitoring, and early therapeutic intervention in high-risk patients. Nevertheless, several limitations remain. Biomarker concentrations may vary according to patient population, timing of sample collection, severity of sepsis, underlying chronic kidney disease, and laboratory methodology. In addition, the relatively high cost of commercial assays and limited availability in many healthcare systems continue to restrict widespread implementation. Consequently, current evidence supports using [TIMP-2]·[IGFBP7] as part of an integrated clinical assessment rather than as a standalone diagnostic test, with future research focusing on standardized cutoff values, external validation, and incorporation into precision medicine algorithms for SA-AKI management. [33]

Functional Biomarkers

Cystatin C

Cystatin C is a 13-kDa cysteine protease inhibitor produced at a constant rate by all nucleated cells and freely filtered through the glomerular membrane. Unlike serum creatinine, its production is largely independent of muscle mass, age, sex, and dietary protein intake, making it a more reliable indicator of glomerular filtration rate in critically ill patients. Following filtration, cystatin C is almost completely reabsorbed and metabolized by proximal tubular epithelial cells without significant tubular secretion. Consequently, increased serum cystatin C reflects an early reduction in glomerular filtration, whereas urinary cystatin C indicates proximal tubular dysfunction. In patients with sepsis-associated acute kidney injury (SA-AKI), serum cystatin C often rises 24–48 hours before serum creatinine, enabling earlier recognition of renal impairment. Several studies have demonstrated that elevated cystatin C is associated with AKI severity, the need for renal replacement therapy, prolonged hospitalization, and increased mortality, supporting its value as both a diagnostic and prognostic biomarker. [34]

Proenkephalin (PENK)

Proenkephalin (PENK) is an emerging functional biomarker that reflects real-time glomerular filtration. It is a stable precursor fragment of enkephalins, endogenous opioid peptides that are continuously released into the circulation and freely filtered by the kidneys. Unlike serum creatinine, PENK concentrations are minimally affected by muscle mass, inflammatory status, or fluid overload, making it particularly attractive for use in septic patients. Recent clinical studies have shown that plasma PENK levels increase very early during declining renal function and correlate closely with measured glomerular filtration rate. Elevated PENK concentrations have been associated with early AKI development, persistent renal dysfunction, renal replacement therapy, and mortality in critically ill patients with sepsis. Because PENK reflects functional impairment before significant creatinine elevation, it has emerged as one of the most promising next-generation biomarkers for early kidney function assessment. [35]

Comparison with Conventional Functional Markers

Compared with serum creatinine and blood urea nitrogen, functional biomarkers such as cystatin C and proenkephalin provide a more sensitive assessment of early renal dysfunction. Serum creatinine may remain within the normal range despite substantial nephron injury because of delayed accumulation and its dependence on muscle metabolism, while blood urea nitrogen is strongly influenced by protein intake, catabolic state, gastrointestinal bleeding, hydration status, and hepatic function. In contrast, cystatin C provides a more accurate estimate of glomerular filtration in critically ill patients, whereas proenkephalin appears to reflect real-time changes in renal filtration with minimal interference from non-renal factors. Nevertheless, both biomarkers primarily

indicate functional decline rather than direct structural injury and therefore are best interpreted alongside tubular injury and inflammatory biomarkers to provide a comprehensive evaluation of SA-AKI. [36]

Clinical Significance and Future Perspectives

Functional biomarkers represent an important bridge between conventional renal function tests and emerging molecular biomarkers. Their ability to detect subtle reductions in glomerular filtration before significant creatinine elevation may facilitate earlier diagnosis, improve risk stratification, and support timely therapeutic interventions in patients with sepsis. However, widespread clinical implementation requires further validation in large multicenter studies, standardized assay methodologies, and clearly defined diagnostic cutoff values across different patient populations. Future precision medicine strategies are likely to integrate functional biomarkers with structural injury markers, inflammatory cytokines, endothelial biomarkers, and clinical prediction models to achieve more accurate diagnosis and individualized management of SA-AKI. [37]

Inflammatory Biomarkers

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine that plays a central role in the pathogenesis of sepsis and sepsis-associated acute kidney injury (SA-AKI). It is produced primarily by monocytes, macrophages, endothelial cells, and renal tubular epithelial cells following activation by pathogen-associated and damage-associated molecular patterns. IL-6 stimulates hepatic synthesis of acute-phase proteins, enhances leukocyte recruitment, promotes endothelial activation, and contributes to coagulation abnormalities and microvascular dysfunction. In SA-AKI, elevated circulating IL-6 concentrations are associated with increased inflammatory burden, tubular injury, endothelial dysfunction, and impaired renal perfusion. Clinical studies consistently demonstrate that high IL-6 levels correlate with AKI severity, progression to multiple organ dysfunction, need for renal replacement therapy, and increased mortality. Because IL-6 rises rapidly during the early phase of sepsis, it has emerged as a valuable biomarker for early risk stratification, although its specificity is limited because it is elevated in numerous inflammatory disorders. [38]

Interleukin-10 (IL-10)

Interleukin-10 (IL-10) is the principal anti-inflammatory cytokine involved in regulating immune homeostasis during sepsis. Produced mainly by regulatory T cells, macrophages, dendritic cells, and B lymphocytes, IL-10 suppresses the synthesis of pro-inflammatory cytokines, inhibits antigen presentation, and limits excessive immune activation. While early IL-10 production protects tissues from inflammatory injury, sustained elevation contributes to immune paralysis, impaired pathogen clearance, and increased susceptibility to secondary infections. In patients with SA-AKI, elevated IL-10 concentrations have been associated with disease severity, persistent kidney injury, prolonged intensive care unit stay, and mortality. Importantly, the balance between IL-6 and IL-10 appears to better reflect the dynamic immune response than either cytokine alone, highlighting the value of combined inflammatory profiling for prognostic assessment in septic patients. [39]

Tumor Necrosis Factor-α (TNF-α)

Tumor necrosis factor-α (TNF-α) is one of the earliest cytokines released following activation of the innate immune system during sepsis. It initiates a cascade of inflammatory events by stimulating cytokine production, endothelial activation, leukocyte adhesion, nitric oxide synthesis, and apoptosis of renal tubular epithelial cells. Experimental studies have demonstrated that TNF-α contributes directly to microvascular dysfunction, oxidative stress, mitochondrial injury, and impaired tubular transport, all of which participate in the development of SA-AKI. Elevated circulating TNF-α levels have been associated with increased disease severity and adverse clinical outcomes; however, because of its rapid release and short biological half-life, its isolated clinical utility as a diagnostic biomarker remains limited. Nevertheless, TNF-α remains an important mechanistic biomarker reflecting the intensity of systemic inflammatory activation during sepsis. [40]

Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is a pro-inflammatory cytokine belonging to the IL-1 family and is produced predominantly by activated macrophages and injured renal tubular epithelial cells. Urinary IL-18 has attracted considerable interest as an early biomarker of tubular injury because it increases before serum creatinine in various forms of acute kidney injury, including SA-AKI. Elevated urinary IL-18 concentrations correlate with tubular inflammation, oxidative stress, and activation of inflammasome pathways,

making it a biologically plausible indicator of structural kidney injury. Several studies have reported that IL-18 predicts severe AKI, requirement for renal replacement therapy, and mortality in critically ill patients, although variability in assay methodology and overlap with other inflammatory conditions continue to limit routine clinical implementation. [41]

Monocyte Chemoattractant Protein-1 (MCP-1)

Monocyte chemoattractant protein-1 (MCP-1), also known as CCL2, is a chemokine responsible for recruiting monocytes and macrophages to sites of inflammation. During sepsis, renal tubular epithelial cells and endothelial cells produce MCP-1 in response to inflammatory stimulation, resulting in leukocyte infiltration and amplification of local renal injury. Increased urinary and plasma MCP-1 concentrations have been associated with tubular inflammation, progression of AKI, and poor clinical outcomes. Because MCP-1 reflects active inflammatory cell recruitment rather than established renal dysfunction, it may complement structural and functional biomarkers in identifying patients with ongoing immune-mediated kidney injury. [42]

Clinical Value of Inflammatory Biomarkers

Inflammatory biomarkers provide valuable insights into the immune dysregulation that characterizes SA-AKI and complement conventional indicators of renal function by identifying underlying biological mechanisms before overt functional impairment develops. However, individual cytokines often lack disease specificity because they are influenced by systemic inflammation, trauma, surgery, autoimmune disorders, and other critical illnesses. Consequently, current evidence supports combining inflammatory biomarkers with tubular injury markers, functional biomarkers, endothelial injury markers, and clinical severity scores to improve diagnostic accuracy and prognostic assessment. Such integrated inflammatory profiling represents an important component of future precision medicine strategies aimed at identifying distinct biological subphenotypes of SA-AKI and guiding individualized therapeutic interventions. [43]

Endothelial and Immune Biomarkers

Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR)

Soluble urokinase-type plasminogen activator receptor (suPAR) is a circulating glycoprotein released from activated immune cells, including neutrophils, monocytes, macrophages, and T lymphocytes, during systemic inflammation. Elevated suPAR concentrations reflect chronic immune activation and have emerged as a promising biomarker for predicting acute kidney injury across various clinical settings, including sepsis. In SA-AKI, increased suPAR levels correlate with disease severity, endothelial dysfunction, systemic inflammation, and poor clinical outcomes. Experimental evidence suggests that suPAR may not only serve as a biomarker but also participate directly in kidney injury by activating podocyte β3-integrin signaling, promoting oxidative stress, and enhancing inflammatory responses. High plasma suPAR concentrations have been associated with an increased risk of AKI development, persistent renal dysfunction, renal replacement therapy, and mortality, making it a promising candidate for early risk stratification in critically ill septic patients. [44]

Angiopoietin-2 (Ang-2)

Angiopoietin-2 is an endothelial-derived growth factor that regulates vascular permeability and endothelial stability through its interaction with the Tie2 receptor. Under physiological conditions, angiopoietin-1 maintains endothelial integrity, whereas Ang-2 antagonizes this protective signaling, promoting endothelial activation, vascular leakage, inflammation, and microvascular dysfunction. During sepsis, circulating Ang-2 concentrations increase markedly and correlate with the severity of endothelial injury and multiple organ dysfunction. Elevated Ang-2 levels have consistently been associated with SA-AKI development, progression to septic shock, requirement for organ support, and mortality. Because endothelial dysfunction is a central mechanism underlying septic organ injury, Ang-2 has attracted considerable attention as both a prognostic biomarker and a potential therapeutic target for preserving microvascular integrity. [45]

Syndecan-1

Syndecan-1 is a major component of the endothelial glycocalyx, a protective carbohydrate-rich layer that maintains vascular barrier function and regulates leukocyte-endothelial interactions. During sepsis, inflammatory mediators, oxidative stress, and enzymatic degradation cause shedding of the glycocalyx, releasing syndecan-1 into the circulation. Elevated plasma syndecan-1 concentrations therefore reflect endothelial injury and glycocalyx degradation, both of which contribute to increased vascular permeability, tissue edema, impaired microcirculation, and organ dysfunction. In patients with SA-AKI, increased syndecan-1

levels have been associated with greater illness severity, progression of renal injury, and poor clinical outcomes, highlighting its potential value as a biomarker of endothelial damage rather than renal injury alone. [46]

High-Mobility Group Box-1 (HMGB1)

High-mobility group box-1 (HMGB1) is a nuclear DNA-binding protein that functions as a damage-associated molecular pattern (DAMP) when released from injured or necrotic cells. Unlike early inflammatory cytokines, HMGB1 is considered a late mediator of sepsis and contributes to sustained inflammation by activating pattern-recognition receptors such as Toll-like receptors and the receptor for advanced glycation end products (RAGE). In SA-AKI, HMGB1 amplifies inflammatory signaling, promotes endothelial dysfunction, enhances oxidative stress, and induces apoptosis of renal tubular epithelial cells. Elevated circulating HMGB1 concentrations have been associated with persistent inflammation, severe AKI, and increased mortality, making this molecule an attractive biomarker of ongoing tissue injury and a potential therapeutic target in septic organ dysfunction. [47]

Clinical Relevance of Endothelial and Immune Biomarkers

Endothelial and immune biomarkers provide complementary information that cannot be obtained from conventional functional or tubular injury markers alone. Whereas biomarkers such as NGAL and KIM-1 primarily reflect tubular epithelial damage, endothelial biomarkers identify vascular injury and microcirculatory dysfunction, and immune biomarkers characterize the intensity of systemic inflammatory activation. Because endothelial dysfunction and immune dysregulation are fundamental mechanisms driving SA-AKI, integrating these biomarkers with functional, structural, and inflammatory markers may substantially improve early diagnosis, biological phenotyping, prognostic assessment, and individualized management. Future precision medicine strategies are expected to incorporate endothelial biomarkers into multimarker panels capable of identifying distinct pathophysiological subgroups and guiding targeted therapeutic interventions. [48]

Conclusion

Biomarker development is reshaping the diagnosis and management of sepsis-associated acute kidney injury by moving beyond delayed functional indicators toward earlier and more mechanistically informative measures of renal stress, tubular damage, inflammation, endothelial dysfunction, and impaired filtration. Although serum creatinine and urine output remain essential in routine practice, emerging biomarkers such as NGAL, KIM-1, L-FABP, cystatin C, proenkephalin, and [TIMP-2]·[IGFBP7] may improve early detection, risk stratification, and prognostic assessment. Their greatest clinical value is likely to arise from integrated multimarker panels combined with clinical data and precision medicine approaches rather than from isolated measurements. Standardized assays, validated thresholds, multicenter studies, and evidence of improved patient outcomes are still required before widespread implementation.

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