Prognostic Utility of Leukocyte Ratios in Critically Ill Patients with Sepsis-Associated Acute Kidney Injury

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Abstract

Background: Sepsis-associated acute kidney injury (SA-AKI) represents one of the most severe and frequent complications encountered in critically ill patients, contributing substantially to short- and long-term morbidity and mortality. The pathophysiology of SA-AKI is complex and extends beyond hemodynamic alterations to include profound immune dysregulation, systemic inflammation, endothelial dysfunction, and microcirculatory impairment. Traditional prognostic markers and severity scores often lack sensitivity for early risk stratification and dynamic monitoring of immune status in this population. Leukocyte-derived ratios obtained from routine complete blood counts—such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)—have emerged as potential surrogate markers reflecting the balance between innate immune activation and adaptive immune suppression during sepsis. Their accessibility, low cost, and reproducibility make them attractive candidates for bedside prognostication in critically ill patients with SA-AKI.

Aim: This review aims to critically evaluate the prognostic utility of leukocyte ratios in critically ill patients with sepsis-associated acute kidney injury. Specifically, it synthesizes current evidence regarding their association with mortality, severity of renal injury, need for renal replacement therapy, and renal recovery. In addition, this review explores the biological rationale underlying these ratios, assesses their performance in comparison with established biomarkers and scoring systems, and discusses their potential role in clinical decision-making and risk stratification.

Conclusion: Accumulating evidence suggests that leukocyte ratios, particularly NLR, PLR, and MLR, are independently associated with adverse outcomes in patients with SA-AKI, including increased mortality and poorer renal prognosis. These indices appear to capture key aspects of sepsis-induced immune imbalance and may provide complementary prognostic information beyond conventional clinical parameters. However, heterogeneity in study design, timing of measurement, cutoff values, and adjustment for confounders limits their immediate clinical integration. Further prospective, standardized studies are required to validate optimal thresholds, evaluate dynamic changes over time, and determine how leukocyte ratios can be incorporated into multimodal prognostic frameworks. When interpreted within appropriate clinical context, leukocyte ratios hold promise as practical, low-cost tools to enhance risk stratification and guide management strategies in critically ill patients with sepsis-associated acute kidney injury.

Keywords: *Leukocyte Ratios, Critically Ill Patients, Sepsis-Associated Acute Kidney Injury*

Introduction

Sepsis-associated acute kidney injury (SA-AKI) is one of the most common and severe complications encountered in critically ill patients, occurring in up to half of septic individuals admitted to intensive care units (ICUs). The presence of AKI in sepsis is independently associated with increased short-term mortality, prolonged ICU stay, higher healthcare costs, and a greater risk of long-term renal dysfunction. Despite improvements in supportive care, outcomes in patients with SA-AKI remain poor, emphasizing the need for improved prognostic tools that can aid early risk stratification and clinical decision-making in this high-risk population [1].

The adoption of the Sepsis-3 definition and Kidney Disease: Improving Global Outcomes (KDIGO) criteria has enhanced diagnostic consistency for both sepsis and AKI. However, these frameworks primarily focus on clinical and biochemical thresholds and offer limited insight into the underlying biological heterogeneity that characterizes septic patients. In particular, they do not adequately capture the immune dysregulation that plays a central role in the development, progression, and resolution of SA-AKI, nor do they reliably predict individual patient trajectories or renal recovery [2].

The pathophysiology of SA-AKI is now recognized as a complex interplay between systemic inflammation, immune dysfunction, endothelial injury, microcirculatory alterations, and metabolic reprogramming. Experimental and clinical studies have demonstrated that renal hypoperfusion alone does not fully explain kidney injury in sepsis. Instead, dysregulated immune responses—characterized by excessive activation of innate immunity alongside suppression of adaptive immune function—contribute to tubular injury, endothelial dysfunction, and impaired cellular repair mechanisms within the kidney [3].

Sepsis induces marked quantitative and functional changes in circulating immune cells. Neutrophil activation and delayed apoptosis promote tissue injury through the release of reactive oxygen species and proteolytic enzymes, while profound lymphocyte apoptosis leads to immune paralysis and increased susceptibility to secondary infections. Monocyte dysfunction further impairs antigen presentation and cytokine signaling. Platelet activation and interaction with leukocytes exacerbate microvascular thrombosis and inflammation, processes that are particularly detrimental to renal microcirculation in SA-AKI [4].

Conventional biomarkers used to diagnose and stage AKI, such as serum creatinine and urine output, are limited by delayed responsiveness and poor specificity in septic patients. Novel renal biomarkers including neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 have shown promise for early detection but remain expensive, variably available, and inconsistently validated for prognostic use in routine ICU practice. Likewise, global severity scores such as SOFA and APACHE II provide overall risk estimates but may fail to reflect immune status or predict kidney-specific outcomes in patients with sepsis [5].

In recent years, leukocyte-derived ratios obtained from routine complete blood counts have emerged as potential surrogate markers of systemic inflammation and immune imbalance. Ratios such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio integrate information from multiple immune cell populations and may better represent the host response to sepsis than isolated leukocyte counts. These indices are inexpensive, rapidly available, and easily repeatable, making them attractive tools for bedside prognostication in critically ill patients [6].

Several observational studies have reported associations between elevated leukocyte ratios and adverse outcomes in septic populations, including increased mortality, greater severity of AKI, higher need for renal replacement therapy, and reduced likelihood of renal recovery. However, the prognostic performance of these ratios in SA-AKI remains inconsistent across studies, with heterogeneity in timing of measurement, cutoff values, and adjustment for confounding factors. Moreover, their biological plausibility and incremental value beyond established clinical parameters have not been comprehensively synthesized [7].

Aim and Research Gap

The aim of this review is to critically evaluate the prognostic utility of leukocyte ratios in critically ill patients with sepsis-associated acute kidney injury. By integrating mechanistic insights with available clinical evidence, this review seeks to address current gaps regarding the predictive value, limitations, and clinical applicability of leukocyte ratios, and to clarify their potential role within multimodal prognostic frameworks for SA-AKI [8].

Immunopathological Basis of Leukocyte Ratios in Sepsis-Associated Acute Kidney Injury

Sepsis is characterized by a dysregulated host immune response to infection, resulting in simultaneous hyperinflammation and immune suppression. This dual-phase immune response plays a pivotal role in the development of organ dysfunction, including acute kidney injury. In the early phase of sepsis, excessive activation of innate immune pathways leads to widespread cytokine release, endothelial injury, and microvascular dysfunction, while later phases are dominated by immune exhaustion and impaired pathogen clearance. These immune alterations directly influence circulating leukocyte populations and provide the biological foundation for leukocyte-derived ratios as prognostic markers in sepsis-associated AKI [9].

Neutrophils are central mediators of the early inflammatory response in sepsis. Sepsis induces neutrophilia through bone marrow stimulation and delayed neutrophil apoptosis, leading to sustained circulation of activated neutrophils. These cells contribute to renal injury via the release of reactive oxygen species, proteases, and neutrophil extracellular traps, which exacerbate tubular epithelial damage and microvascular obstruction. Excessive neutrophil activation has been consistently linked to the severity of sepsis and the development of AKI, supporting the prognostic relevance of neutrophil-dominant indices such as the neutrophil-to-lymphocyte ratio [10].

In contrast, lymphopenia is a hallmark of sepsis-induced immune suppression and is strongly associated with adverse outcomes. Accelerated apoptosis of CD4+ and CD8+ T lymphocytes occurs early in sepsis and correlates with impaired adaptive immunity, increased susceptibility to secondary infections, and failure of organ recovery. In patients with SA-AKI, persistent lymphopenia reflects an inability to restore immune homeostasis and has been associated with increased mortality and poor renal recovery, thereby amplifying the prognostic signal of leukocyte ratios that incorporate lymphocyte counts [11].

Monocytes play a critical role in antigen presentation, cytokine signaling, and coordination of innate and adaptive immune responses. Sepsis is associated with both quantitative and functional monocyte abnormalities, including reduced human leukocyte antigen–DR expression and impaired cytokine production. Monocyte dysfunction contributes to immune paralysis and prolonged inflammation, which may perpetuate renal injury. The monocyte-to-lymphocyte ratio has therefore been proposed as a marker of immune imbalance, reflecting the relative dominance of innate immune activation over adaptive immune suppression in critically ill septic patients [12].

Platelets, traditionally recognized for their role in hemostasis, are now understood to be active participants in the immune response to sepsis. Platelet activation promotes leukocyte recruitment, endothelial adhesion, and microthrombus formation within the renal microvasculature. Thrombocytopenia is common in sepsis and is independently associated with increased mortality and organ failure, including AKI. Ratios incorporating platelet counts, such as the platelet-to-lymphocyte ratio, may therefore reflect the interplay between coagulation, inflammation, and immune suppression that characterizes SA-AKI [13].

Leukocyte-derived ratios integrate changes across multiple immune cell lineages, providing a composite measure of systemic immune dysregulation. Unlike single-cell counts, these ratios capture the balance between pro-inflammatory effector mechanisms and anti-inflammatory or immunosuppressive processes. This integrative nature may explain why leukocyte ratios often demonstrate stronger associations with clinical outcomes than individual leukocyte parameters in septic populations, including those with acute kidney injury [14].

Importantly, immune responses in sepsis are dynamic rather than static. Temporal changes in leukocyte ratios may reflect evolving immune states, treatment responses, and progression or resolution of organ dysfunction. Persistent elevation or worsening of leukocyte ratios over time has been associated with

unfavorable outcomes, whereas normalization may indicate immune recovery and improved prognosis. This dynamic behavior supports the potential utility of serial leukocyte ratio measurements for monitoring disease trajectory in SA-AKI [15].

Neutrophil-to-Lymphocyte Ratio and Prognostic Outcomes in Sepsis-Associated Acute Kidney Injury

The neutrophil-to-lymphocyte ratio (NLR) is one of the most extensively studied leukocyte-derived indices in sepsis and critical illness. It reflects the relative dominance of innate immune activation over adaptive immune suppression, a hallmark of sepsis-associated immune dysregulation. Because both neutrophilia and lymphopenia are independently associated with adverse outcomes, their integration into a single ratio amplifies prognostic sensitivity. In patients with sepsis-associated AKI, elevated NLR has been consistently linked to increased illness severity and worse clinical outcomes [16].

Several observational studies in critically ill populations have demonstrated a strong association between elevated admission NLR and short-term mortality in sepsis. In patients with SA-AKI, higher NLR values at ICU admission or at the time of AKI diagnosis have been associated with increased 28-day and in-hospital mortality, even after adjustment for established severity scores such as SOFA and APACHE II. These findings suggest that NLR provides prognostic information that is at least partially independent of global illness severity and traditional risk factors [17].

Beyond mortality, NLR has been correlated with the severity and progression of acute kidney injury in septic patients. Higher NLR values have been associated with more advanced KDIGO AKI stages, greater need for renal replacement therapy, and prolonged duration of renal dysfunction. The association between elevated NLR and severe AKI likely reflects intensified inflammatory injury to the renal microvasculature and tubular epithelium, mediated by excessive neutrophil activation and impaired immune regulation [18].

Dynamic assessment of NLR over time appears to further enhance its prognostic utility. Studies evaluating serial NLR measurements have shown that persistently elevated or rising NLR during the early ICU course is associated with increased mortality and failure of renal recovery. In contrast, a declining NLR trajectory has been linked to improved survival and better renal outcomes, suggesting that temporal trends in NLR may serve as a marker of treatment response and immune restoration in SA-AKI [19].

Despite its clinical appeal, the use of NLR in SA-AKI is limited by variability in reported cutoff values across studies. Differences in patient populations, timing of measurement, infection sources, and analytical methods have resulted in a wide range of proposed thresholds for risk stratification. This heterogeneity complicates direct comparison between studies and limits the immediate translation of NLR into standardized clinical decision-making algorithms [20].

Importantly, NLR should not be interpreted in isolation. Factors such as corticosteroid therapy, hematologic disorders, malignancy, and chronic inflammatory conditions can influence neutrophil and lymphocyte counts independently of sepsis severity. In critically ill patients with SA-AKI, integrating NLR with clinical context, severity scores, and other laboratory parameters is essential to avoid misinterpretation and overestimation of its prognostic significance [21].

Overall, current evidence supports NLR as a readily available and biologically plausible prognostic marker in sepsis-associated AKI. Its strongest utility appears to lie in early risk stratification and dynamic monitoring rather than single time-point prediction. Further prospective studies are needed to define standardized cutoff values, optimal timing of measurement, and the incremental benefit of NLR when combined with other prognostic tools in critically ill patients with SA-AKI [22].

Platelet-to-Lymphocyte Ratio and Renal Outcomes in Sepsis-Associated Acute Kidney Injury

The platelet-to-lymphocyte ratio (PLR) integrates two clinically meaningful septic phenotypes: platelet activation/consumption (reflecting thrombo-inflammation and microvascular injury) and lymphopenia (reflecting adaptive immune suppression). In SA-AKI, where endothelial injury and microcirculatory dysfunction are central mechanisms, PLR is biologically plausible as a prognostic signal because it mirrors the interaction between coagulation and immune dysregulation that contributes to renal hypoxia, tubular stress, and impaired repair. Platelet–leukocyte crosstalk and sepsis-associated thrombocytopenia have repeatedly been linked to organ failure burden and mortality, making platelet-based ratios attractive for

bedside risk stratification. [13]

In critically ill cohorts, PLR has shown associations with mortality and severity endpoints, but interpretation in SA-AKI must account for platelet behavior in sepsis, which may be biphasic (early activation with subsequent consumption). A high PLR may reflect a strong inflammatory response with relative preservation of platelets but profound lymphopenia, whereas a low PLR in advanced sepsis may reflect severe thrombocytopenia and immune exhaustion. This complexity means PLR should be viewed as a marker of immune–hemostatic balance rather than a simple "higher is worse" index across all clinical phases. [4]

Evidence increasingly supports PLR as a prognostic indicator in SA-AKI specifically. For example, a 2026 multicenter retrospective study reported that baseline PLR and dynamic PLR changes during hospitalization were significant predictors of mortality in patients with septic AKI, highlighting potential value not only at admission but also as a serial monitoring tool. These findings align with the concept that trajectories of immune–coagulation indices may better reflect evolving risk than single time-point measurements, particularly during the early ICU course when treatment response and immune reversal are most informative. [23]

PLR also appears relevant in patients with severe AKI requiring extracorporeal support. A 2023 study in critically ill patients with severe AKI undergoing continuous kidney replacement therapy found an association between PLR and in-hospital mortality, suggesting that platelet–lymphocyte balance retains prognostic meaning even in advanced renal dysfunction and high-intensity ICU settings. Although not restricted to SA-AKI alone, these data are clinically useful because septic shock is a leading indication for continuous kidney replacement therapy, and the biologic pathways captured by PLR are highly active in that subgroup. [24]

From a renal-outcome standpoint, PLR may plausibly relate to the need for renal replacement therapy and impaired renal recovery via platelet-driven microvascular thrombosis and immune-mediated endothelial injury. Platelet activation promotes microthrombi, impairs renal capillary flow, and amplifies leukocyte recruitment, mechanisms that can worsen AKI stage and delay renal recovery. Therefore, PLR could serve as a low-cost adjunct to clinical staging (KDIGO) and organ failure scoring (SOFA) when identifying patients at heightened risk of persistent kidney dysfunction. [13]

Despite promise, key limitations remain before PLR can be routinely implemented for SA-AKI prognostication. Cutoff values vary substantially across studies due to differences in case mix, timing (admission vs AKI onset vs day-3/day-5), platelet transfusion practices, and confounding from liver disease, disseminated intravascular coagulation, or hematologic disorders. Clinically, PLR is best interpreted alongside platelet count trends, coagulation parameters, infection source control, and immunomodulating therapies (e.g., corticosteroids), with future prospective studies needed to standardize timing, validate thresholds, and test incremental value in multimarker models for SA-AKI. [3]

Monocyte-to-Lymphocyte Ratio and Composite Inflammatory Indices in Sepsis-Associated AKI

Monocyte-to-lymphocyte ratio (MLR) has attracted attention as a clinically accessible marker integrating two key components of sepsis immunobiology: monocyte-line innate activation/dysfunction and sepsis-associated lymphopenia. From an internal medicine perspective, this ratio is appealing because it can reflect the "immune imbalance" phenotype that often accompanies worse organ dysfunction, persistent inflammation, secondary infections, and delayed recovery. In SA-AKI, these pathways are particularly relevant because maladaptive monocyte responses and lymphocyte depletion contribute to endothelial injury, microcirculatory compromise, and impaired tubular repair—mechanisms tightly linked with AKI persistence and poor outcomes. [25]

Clinical evidence supports MLR as a useful inflammatory index in critically ill patients at risk of AKI and suggests potential relevance to septic AKI. In a retrospective ICU cohort (n≈1500), Jiang and colleagues reported that MLR was strongly associated with AKI occurrence and showed good discrimination for AKI development, with an identified cutoff around 0.693 (while noting limited predictive ability for mortality). While this study was not restricted to sepsis-only AKI, it provides mechanistic and clinical support that monocyte–lymphocyte balance is linked to kidney injury in critical illness, and it supports the rationale

for extending MLR evaluation specifically to SA-AKI prognostication models. [26]

More directly relevant to SA-AKI, whole blood–derived marker studies using large ICU databases have evaluated MLR alongside other ratios for mortality prediction. A retrospective cohort analysis in SA-AKI patients from the MIMIC-IV database evaluated multiple indices (including NLR, PLR, MLR, SII, and SIRI) and found that higher levels of these inflammatory markers were significantly associated with increased all-cause mortality, with robustness supported by methods such as restricted cubic splines and propensity score approaches. This type of analysis is clinically important because it evaluates MLR not in isolation but in the context of competing inflammatory indices and real-world ICU confounding, which better reflects how these tools might be used at the bedside. [27]

Because single ratios may oversimplify a complex immune–thrombotic syndrome, composite indices derived from CBC components have gained traction, particularly the systemic immune-inflammation index (SII: platelets × neutrophils / lymphocytes) and systemic inflammation response index (SIRI: neutrophils × monocytes / lymphocytes). In a large SA-AKI cohort study, SII demonstrated a non-linear (J-shaped) relationship with short-term mortality, suggesting that both excessively low and excessively high immune-inflammatory states may confer risk. Clinically, this supports the idea that risk is not purely "more inflammation = worse," but rather that extremes of immune activation or immune suppression/consumption may both identify vulnerable SA-AKI phenotypes. [28]

Additional composite markers have also emerged, including the aggregate index of systemic inflammation (AISI: neutrophils × monocytes × platelets / lymphocytes), which integrates three innate/hemostatic components against lymphocyte-mediated adaptive capacity. A Scientific Reports analysis in SA-AKI using MIMIC-IV data reported that higher AISI at admission was associated with higher 30-, 90-, 180-day, and 1-year mortality, with non-linear risk patterns and consistent associations across subgroups. These findings strengthen the argument that multi-lineage composite indices may better capture the intertwined inflammatory and thrombotic biology of SA-AKI than any single leukocyte ratio alone. [29]

Despite encouraging associations, MLR and composite indices share important limitations that must be addressed before routine ICU implementation. Timing is critical (ICU admission vs AKI onset vs 24–48 h trends), and indices are easily confounded by immunosuppressive therapies (notably corticosteroids), hematologic disease, malignancy, bone marrow suppression, transfusions, and sepsis-related consumptive coagulopathy. Practically, the most defensible approach is to interpret MLR/SII/SIRI/AISI as *adjunctive* signals alongside KDIGO staging, SOFA trends, lactate kinetics, hemodynamic context, and infection control milestones, while prioritizing prospective validation of standardized measurement windows and clinically actionable thresholds in SA-AKI. [28]

Timing, Cutoffs, and Dynamic Trends—Optimizing Leukocyte Ratio Measurement for Prognostication in SA-AKI

In critically ill patients with sepsis-associated AKI, the prognostic value of leukocyte ratios is highly dependent on *when* they are measured. Sepsis is a dynamic syndrome in which leukocyte subsets can change substantially over hours due to evolving infection control, fluid resuscitation, vasopressor exposure, organ support, and immunomodulating therapies. Therefore, a single admission value may reflect baseline immune state and pre-ICU trajectory, whereas subsequent measurements may better represent treatment response and the direction of immune dysregulation (reversal vs persistence). This time-dependence explains why studies increasingly evaluate both baseline ratios and their early ICU kinetics when predicting mortality and kidney-related endpoints. [30]

For NLR, evidence supports the concept that *dynamic change* adds prognostic information beyond a single time-point. A cohort study specifically evaluating NLR dynamics in septic AKI reported that longitudinal patterns were associated with outcomes, reinforcing the idea that persistent elevation or adverse trajectories may identify ongoing immune injury and higher risk. Clinically, this supports incorporating NLR into structured reassessments (e.g., admission and early follow-up values) rather than relying solely on admission results. [31]

A similar principle has been demonstrated in AKI populations receiving high-intensity organ support. In patients undergoing continuous kidney replacement therapy, early changes in NLR during the initial phase

of therapy were independently associated with mortality, suggesting that ratio kinetics can remain informative even when renal failure is advanced and extracorporeal therapies may influence inflammatory profiles. For SA-AKI, this is particularly relevant because continuous modalities are frequently used in septic shock and may coincide with rapidly changing immune states during the first 48–72 hours of ICU care. [32]

For PLR, interpretation is more nuanced because platelet counts in sepsis reflect both inflammatory activation and consumptive coagulopathy, and may be altered by transfusion practices and disseminated intravascular coagulation physiology. Nonetheless, recent evidence in septic AKI indicates that baseline PLR and its *dynamic change* during hospitalization can predict mortality, supporting serial measurement rather than one-off thresholds. Practically, PLR should be interpreted alongside absolute platelet trends and coagulation context, because low PLR may indicate platelet consumption in advanced sepsis while high PLR may reflect preserved platelets with severe lymphopenia. [33]

One of the main barriers to clinical implementation is the lack of standardized cutoff values across studies. Thresholds vary due to heterogeneity in case mix (septic shock vs sepsis without shock), timing (ICU admission vs AKI diagnosis), and analytic strategies (categorical cutoffs vs spline-based modeling). Large retrospective SA-AKI cohorts have demonstrated non-linear risk patterns for CBC-derived indices such as SII, implying that "higher is worse" may not apply uniformly across the full biological range and that extremes on either end may represent different high-risk phenotypes. This directly argues for outcome-based, cohort-specific calibration rather than importing a single universal cutoff into all ICUs. [34]

From an internal medicine workflow perspective, the most defensible measurement strategy for prognostication is a standardized early window combined with reassessment. A practical approach supported by the direction of the evidence is to document leukocyte ratios at ICU admission (or at SA-AKI recognition) and then re-check within an early interval (commonly within the next 24–72 hours) to capture kinetics, while interpreting values in the context of confounders such as corticosteroids, hematologic disease, chemotherapy, recent transfusion, and evolving coagulopathy. Future prospective studies should prioritize harmonized timepoints, reporting of treatment confounders, and validation of clinically actionable thresholds integrated into multimarker models (e.g., ratios plus SOFA/KDIGO). [34]

Comparative Prognostic Performance—Leukocyte Ratios vs SOFA/APACHE II and Renal Biomarkers

Severity scoring systems such as SOFA and APACHE II remain foundational for risk stratification in ICU sepsis because they summarize multisystem physiologic derangement and correlate strongly with mortality at the population level. However, these scores were not designed to specifically characterize immune dysregulation or to isolate kidney-centered prognostic trajectories in SA-AKI, and they may perform variably across different septic phenotypes. Consequently, there is increasing interest in whether leukocyte ratios add incremental prognostic value by capturing immune balance (innate predominance vs adaptive suppression) that is not explicitly represented in SOFA/APACHE inputs. [35]

SOFA is particularly relevant to sepsis because it operationalizes organ dysfunction burden and is widely used both clinically and in research. Yet SOFA can be limited for SA-AKI precision: creatinine/urine output contribute directly to the renal component, so prognostic "prediction" may partly reflect downstream recognition of established injury rather than early biologic risk. Leukocyte ratios, in contrast, can change rapidly with immune activation and may provide earlier signals of high-risk immune phenotypes—especially when tracked dynamically—potentially complementing SOFA rather than replacing it. [36]

APACHE II similarly provides a robust global severity framework, but it is influenced by numerous physiologic variables that may fluctuate substantially with early resuscitation and ICU interventions. From an internal medicine viewpoint, this raises a practical question: can a readily repeatable biomarker-like signal (e.g., NLR/PLR/MLR kinetics) improve near-term prognostication beyond a single complex score calculation? In this context, leukocyte ratios are attractive because they are continuously available from routine CBC monitoring, can be trended daily (or more frequently), and may reflect evolving immune state even when overall physiology appears temporarily stabilized by supportive care. [37]

Compared with clinical scores, kidney-specific biomarkers aim to detect renal stress/injury earlier and more directly. NGAL is among the most studied, and a systematic review/meta-analysis focused on sepsis reported that NGAL has value not only for predicting AKI but also shows potential prognostic utility for renal replacement therapy requirement and mortality. In practice, NGAL may outperform leukocyte ratios for *renal injury biology* in settings where it is rapidly available; however, its implementation is limited by assay availability, cost, and variability in cutoffs and sampling matrices (plasma vs urine), whereas leukocyte ratios remain universally accessible. [38]

Cystatin C also has substantial evidence as an alternative renal biomarker with potential advantages over creatinine in dynamic critical illness. In sepsis ICU populations, serum cystatin C has been associated with the development and worsening of AKI, supporting its prognostic relevance when early renal risk identification is needed. Importantly, cystatin C still represents kidney filtration biology rather than immune balance, so it may be most informative when combined with immune-derived markers (ratios/indices) to capture both "host response" and "renal vulnerability." [39]

Overall, the most clinically defensible model is a *complementary* framework: severity scores (SOFA/APACHE II) describe physiologic burden; renal biomarkers (NGAL, cystatin C) reflect kidney stress/filtration; and leukocyte ratios reflect immune phenotype and immune trajectory. The key opportunity—especially for SA-AKI—lies in multimodal prognostic strategies that test whether leukocyte ratios add incremental discrimination and calibration beyond SOFA/APACHE II and beyond kidney biomarkers, using standardized sampling windows and clinically actionable endpoints (mortality, renal replacement therapy, renal recovery). Evidence that cystatin C–derived measures associate with mortality and AKI in sepsis even after adjustment for severity supports this "layered" approach rather than reliance on any single marker class. [40]

Conclusion

Sepsis-associated acute kidney injury remains a major challenge in critical care medicine, driven by complex interactions between infection, immune dysregulation, endothelial injury, and renal vulnerability. In this context, leukocyte-derived ratios obtained from routine complete blood counts have emerged as attractive prognostic tools because they reflect key dimensions of the host immune response while remaining inexpensive, widely available, and easily repeatable. Evidence synthesized in this review indicates that ratios such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and composite inflammatory indices capture biologically meaningful immune phenotypes that are closely linked to adverse outcomes in critically ill patients with sepsis-associated acute kidney injury.

Across studies, elevated leukocyte ratios and unfavorable ratio trajectories are consistently associated with higher mortality, greater severity of renal injury, increased need for renal replacement therapy, and reduced likelihood of renal recovery. Importantly, the prognostic relevance of these indices appears strongest when they are interpreted dynamically rather than as isolated admission values, highlighting the evolving nature of immune responses during sepsis. When integrated with clinical severity scores and kidney-specific biomarkers, leukocyte ratios provide complementary information that may enhance risk stratification beyond traditional approaches alone.

Despite their promise, several limitations currently restrict the routine clinical implementation of leukocyte ratios for prognostication in sepsis-associated acute kidney injury. Heterogeneity in study design, timing of measurement, cutoff values, and adjustment for confounding factors has led to variable findings and limits generalizability. In addition, leukocyte ratios are influenced by numerous clinical factors common in ICU practice, including corticosteroid therapy, hematologic disorders, malignancy, chronic kidney disease, transfusions, and extracorporeal support, necessitating careful contextual interpretation.

Future research should prioritize prospective, multicenter studies with standardized measurement windows, predefined endpoints, and robust adjustment for confounders to clarify the incremental value of leukocyte ratios within multimodal prognostic frameworks. Particular emphasis should be placed on validating dynamic ratio trajectories and determining whether these indices can guide therapeutic decision-making or identify patient subgroups most likely to benefit from targeted interventions. Until such

evidence is available, leukocyte ratios should be viewed as adjunctive markers that enhance, rather than replace, established clinical and biochemical tools in the prognostic assessment of critically ill patients with sepsis-associated acute kidney injury.

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