



Early Recognition of Sepsis-Associated Acute Kidney Injury Through Routine Hematologic Indices

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Abstract

Background: Sepsis-associated acute kidney injury (SA-AKI) is common, develops early, and carries substantial risks of death, kidney replacement therapy, incomplete renal recovery, and chronic kidney disease. Serum creatinine and urine output remain the basis of acute kidney injury diagnosis, but both may identify injury only after clinically important renal stress has occurred. This delay has encouraged interest in rapidly available biomarkers that can support earlier risk recognition.

Main text: Monocyte distribution width (MDW), red cell distribution width (RDW), and the neutrophil-to-lymphocyte ratio (NLR) are derived from the complete blood count and reflect different components of the septic response. MDW captures infection-related variability in monocyte size and activation. RDW reflects anisocytosis arising from inflammation, oxidative stress, disordered iron handling, impaired erythropoiesis, and altered red-cell survival. NLR integrates neutrophilia with stress-associated lymphopenia and therefore represents the balance between innate activation and adaptive immune suppression. These indices are attractive because they are inexpensive, rapidly generated, and require little or no additional blood. Their individual specificity for renal injury is limited, however, and values are affected by age, anemia, transfusion, malignancy, corticosteroids, chronic inflammation, and analyzer-related factors. The most directly relevant clinical study found that models combining MDW, RDW, or NLR with the initial Sequential Organ Failure Assessment score and mean arterial pressure achieved areas under the receiver operating characteristic curve of 0.728, 0.712, and 0.719, respectively. These results indicate moderate discrimination and support integrated multivariable assessment rather than isolated thresholds. Serial NLR may add prognostic information after SA-AKI develops, while evidence for serial MDW and RDW remains less mature.

Conclusion: CBC-derived indices can strengthen early SA-AKI surveillance, particularly in emergency and resource-limited settings, but they should not replace Kidney Disease: Improving Global Outcomes criteria, clinical assessment, or kidney-specific biomarkers. Their most credible role is within a repeated, multivariable risk framework that prompts closer urine-output monitoring, medication review, hemodynamic reassessment, and selective use of renal damage or stress biomarkers. Prospective multicenter validation using Sepsis-3 and standardized SA-AKI definitions is required before universal cutoffs or treatment-triggering algorithms can be recommended.

Keywords: sepsis-associated acute kidney injury, monocyte distribution width, red cell distribution width, neutrophil-to-lymphocyte ratio, biomarkers



Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite advances in recognition and supportive care, it remains a major cause of critical illness, and the timing of antimicrobial therapy, hemodynamic stabilization, source control, and organ support continues to influence outcome [2]. The kidney is particularly vulnerable. Sepsis-associated acute kidney injury (SA-AKI) can appear at presentation, evolve during the first days of admission, or persist beyond the acute septic episode. Its development is associated with greater short-term mortality, prolonged intensive care, kidney replacement therapy, and later chronic kidney disease [3-5].

The clinical definition of SA-AKI is more difficult than it first appears. Sepsis and acute kidney injury (AKI) are both syndromic diagnoses, their temporal relationship is not always clear, and baseline serum creatinine may be unavailable. Published estimates therefore vary according to the sepsis definition, AKI criteria, observation window, and attribution rules [3,6]. Current consensus favors identifying AKI by Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine and urine-output criteria in a patient with sepsis when another cause does not better explain the renal deterioration [3]. This approach provides a necessary common language, but it does not fully solve the problem of early recognition.

Serum creatinine is a functional marker with delayed kinetics. Its concentration is influenced by muscle mass, volume status, creatinine generation, and dilution from resuscitation. Urine output may change earlier but is affected by hemodynamics, diuretics, obstruction, and the accuracy of bedside measurement [7]. A patient may therefore sustain renal stress or structural injury before either diagnostic criterion becomes unequivocal. Kidney-specific biomarkers offer biologic information beyond creatinine, yet cost, turnaround time, platform availability, and uncertain treatment thresholds have limited routine use [17-21].

The complete blood count (CBC) offers a different opportunity. Monocyte distribution width (MDW), red cell distribution width (RDW), and the neutrophil-to-lymphocyte ratio (NLR) are rapidly obtainable indices that reflect immune activation, oxidative stress, erythropoietic disruption, and systemic inflammation. Because the same processes contribute to septic renal dysfunction, these indices may help identify patients whose kidneys are at imminent risk. This narrative review examines the biologic rationale, current clinical evidence, practical strengths, limitations, and potential integration of MDW, RDW, and NLR in the early recognition of SA-AKI.

Clinical Definition and Burden of Sepsis-Associated Acute Kidney Injury

SA-AKI should be regarded as a clinical phenotype rather than a single pathologic lesion. It includes new or worsening AKI arising during sepsis, but renal dysfunction may result from overlapping factors such as hypovolemia, venous congestion, drug toxicity, obstruction, contrast exposure, pre-existing chronic kidney disease, or another acute process. The Acute Disease Quality Initiative has emphasized transparent reporting of both sepsis and AKI criteria, the time window linking the two conditions, baseline kidney function, and competing etiologies [3]. This distinction matters because a biomarker may reflect systemic sepsis severity without being specific to kidney injury.

Contemporary multicenter data confirm that SA-AKI is frequent and heterogeneous. White et al. [4] described variation in onset, trajectory, recovery, and treatment among critically ill patients, while Takeuchi et al. [5] showed that incidence estimates remain sensitive to the definitions applied. A systematic review by Donaldson et al. [6] similarly found that alternative SA-AKI definitions materially alter measured incidence and outcome associations. The clinically important message is stable across studies: severe or persistent SA-AKI identifies a group with high mortality and substantial risk of non-recovery.

The consequences continue after discharge. Sepsis-associated acute kidney disease may persist beyond seven days, and survivors face recurrent AKI, reduced estimated glomerular filtration rate, chronic kidney disease, cardiovascular events, and death [8]. Bidirectional kidney-organ interactions may amplify lung, cardiac, neurologic, and immune dysfunction, while residual renal impairment can modify drug exposure and complicate recovery [9]. Early recognition is therefore not an academic endpoint. It



creates an opportunity to intensify surveillance, correct reversible contributors, adjust nephrotoxic medication, optimize perfusion, and plan follow-up.

Why Early Detection Remains Difficult

The traditional model of septic AKI as simple global renal hypoperfusion followed by widespread acute tubular necrosis is incomplete. AKI may occur despite preserved or increased total renal blood flow, and histologic damage is often patchy and less extensive than the decline in filtration would suggest [7,10]. Functional adaptation, altered intrarenal blood-flow distribution, tubular transport changes, endothelial injury, microvascular shunting, and inflammatory signaling can reduce glomerular filtration without diffuse tubular necrosis.

Sepsis activates pathogen-associated and damage-associated molecular pathways in circulating immune cells, vascular endothelium, and renal tubular epithelium [10-12]. Endothelial dysfunction, glycocalyx loss, leukocyte and platelet adhesion, coagulation activation, and microthrombi produce heterogeneous capillary flow [13]. Mitochondrial injury and reactive oxygen species disrupt tubular energy metabolism, while metabolic downregulation may preserve cell survival at the expense of transport and filtration [14,15]. Apoptosis, pyroptosis, necroptosis, and ferroptosis may contribute in selected settings, but their relative importance in human SA-AKI remains uncertain [16].

These pathways develop before creatinine necessarily rises. Biomarkers of tubular damage, cell-cycle arrest, and glomerular filtration have therefore been studied extensively. Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C, interleukin-18, liver fatty acid-binding protein, and urinary tissue inhibitor of metalloproteinase-2 combined with insulin-like growth factor-binding protein 7 provide potentially useful information, although performance varies with infection, chronic kidney disease, timing, and the outcome selected [17-20]. Limited availability and the absence of a universally accepted biomarker-guided treatment pathway remain practical barriers [20,21].

CBC-derived indices do not solve the specificity problem, but they address accessibility. They can be available with the first blood sample, can be repeated at low marginal cost, and may identify a biologically high-risk state before conventional renal criteria are complete. Their value should therefore be judged as risk enhancers within a clinical model, not as stand-alone renal injury tests.

Biological Basis of Complete Blood Count-Derived Signals

Sepsis produces rapid changes across innate and adaptive immunity. Activated monocytes alter in size and internal complexity, neutrophils are mobilized and delayed in apoptosis, and circulating lymphocytes often decline through redistribution and programmed cell death [11,12]. At the same time, inflammatory cytokines, oxidative injury, nutritional disturbance, altered iron metabolism, renal dysfunction, and transfusion affect erythrocyte production and survival. MDW, NLR, and RDW therefore measure distinct but interconnected consequences of the same dysregulated host response.

Their relationship to SA-AKI is biologically plausible for three reasons. First, the intensity of systemic inflammation is linked to endothelial and tubular stress. Second, the renal microcirculation is exposed directly to activated leukocytes, inflammatory mediators, and immunothrombotic signals. Third, severe sepsis produces parallel immune, hemodynamic, and metabolic abnormalities that may be captured incompletely by any single variable. A composite model can therefore perform better than an isolated blood-cell parameter even when none is kidney specific.

This distinction is essential for interpretation. An abnormal MDW, RDW, or NLR may indicate that a patient with infection is at greater risk of organ dysfunction, but it cannot determine whether the kidney abnormality is caused by sepsis, drug toxicity, obstruction, venous congestion, or another insult. The indices should trigger renal assessment rather than substitute for it.

Monocyte Distribution Width

MDW quantifies variability in circulating monocyte volume. Monocytes respond early to microbial and danger signals, developing morphologic heterogeneity as they activate, differentiate, and interact with endothelium and injured tissue. This variability is detected by compatible automated hematology analyzers and can be reported with the CBC differential [22-26]. MDW is not the monocyte count and is not a soluble inflammatory molecule. It is an analyzer-derived measure of monocyte anisocytosis.



Most MDW research has addressed sepsis detection rather than SA-AKI. In high-risk emergency patients, Crouser et al. [22] found that MDW improved recognition of both Sepsis-2 and Sepsis-3 phenotypes. A prospective multicenter European study showed that MDW contributed diagnostic information alongside C-reactive protein and procalcitonin [23]. Systematic reviews and meta-analyses have supported moderate diagnostic utility and a potentially useful negative predictive role, while also documenting differences among thresholds, settings, reference standards, and analytic methods [24,25]. Reviews of the field emphasize that MDW reflects monocyte activation across diverse infectious causes, which supports its use as a broad sepsis signal rather than a pathogen-specific test [26].

Evidence directly connecting MDW with SA-AKI is much thinner. Pan et al. [27] evaluated patients with sepsis presenting to an emergency department and developed three multivariable models. The model containing MDW, the initial Sequential Organ Failure Assessment (SOFA) score, and mean arterial pressure (MAP) achieved an area under the receiver operating characteristic curve (AUC) of 0.728 (95% confidence interval [CI], 0.668-0.789). MDW remained associated with sepsis-induced AKI after clinical variables were considered. The result is important because MDW was obtained at presentation, but the discrimination was moderate and the study used Sepsis-2 criteria, was retrospective, and was conducted at a single center. External validation under Sepsis-3 and consensus SA-AKI definitions is still needed.

MDW has practical limitations. It is not generated by every hematology platform, and results may vary with analyzer technology, anticoagulant, sample handling, and time from phlebotomy to analysis. Thresholds developed for detecting sepsis cannot automatically be transferred to predicting renal injury. Monocyte disorders, hematologic malignancy, immunosuppressive therapy, and profound leukopenia may also alter performance. MDW is therefore best viewed as an early inflammatory signal that may improve SA-AKI risk estimation when combined with renal and hemodynamic variables.

Red Cell Distribution Width

RDW describes the variability of erythrocyte size. It is conventionally used in anemia evaluation, but elevated RDW also accompanies systemic inflammation, oxidative stress, impaired iron utilization, ineffective erythropoiesis, shortened red-cell survival, nutritional deficiency, chronic kidney disease, and critical illness. These mechanisms are common in sepsis and can intensify during renal dysfunction. The association between RDW and adverse outcomes is consistent across many critically ill populations, but its role in early SA-AKI detection is less established. Zhu et al. [28] found that RDW and NLR were associated with adverse outcomes among hospitalized patients with AKI. In the study by Pan et al. [27], a model combining RDW, initial SOFA score, and MAP yielded an AUC of 0.712 (95% CI, 0.651-0.774) for sepsis-induced AKI. This was slightly lower than the corresponding MDW model, and the overlapping confidence intervals do not justify declaring one marker superior without formal comparison.

RDW is widely available, inexpensive, and analytically familiar, but it changes more slowly than leukocyte indices and is strongly influenced by pre-existing conditions. Iron, vitamin B12, or folate deficiency; recent transfusion; hemolysis; marrow disease; chronic liver disease; malignancy; age; and baseline kidney dysfunction can all raise RDW independently of acute sepsis. A single elevated value may therefore reflect chronic vulnerability rather than a new renal insult. Delta RDW or a trajectory may be more informative in prolonged admission, but evidence for using serial RDW to identify early SA-AKI is insufficient. Its most appropriate role is as a contextual risk marker interpreted alongside hemoglobin, mean corpuscular volume, transfusion history, and previous RDW values.

Neutrophil-to-Lymphocyte Ratio

NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. It integrates two common features of sepsis: neutrophilia related to innate immune activation and lymphopenia associated with stress signaling, redistribution, apoptosis, and immune exhaustion. Because it is derived from the differential count, NLR can be calculated in nearly any clinical laboratory. Several retrospective studies have linked higher NLR with SA-AKI. Bu et al. [29] reported an association between NLR and AKI among patients with sepsis or septic shock. Xie et al. [30] found that

NLR contributed to prediction of sepsis-induced kidney injury, while Xiao et al. [31] used a large public database and double-robust methods to examine initial NLR and platelet-to-lymphocyte ratio in relation to SA-AKI incidence and severity. Pan et al. [27] reported an AUC of 0.719 (95% CI, 0.658-0.780) for a model combining NLR, initial SOFA score, and MAP.

NLR may also provide prognostic information after SA-AKI has developed. Wei et al. [32] associated higher NLR with mortality and disease severity in septic AKI. In a later cohort of 413 patients, a high change in NLR from admission to SA-AKI diagnosis was independently associated with 90-day mortality (adjusted hazard ratio, 2.80; 95% CI, 1.74-4.49), as well as 30-day mortality, kidney replacement therapy, and stage 3 AKI [33]. The AUC for 90-day mortality was 0.685, indicating modest discrimination despite significant association.

A 2025 systematic review and meta-analysis included 29 studies and 102,870 patients across AKI settings [34]. Overall NLR performance for AKI was moderate, with pooled AUC 0.74, sensitivity 0.70, and specificity 0.67. Importantly, the SA-AKI subgroup included five studies and 2,012 patients; the pooled association did not reach conventional statistical significance (odds ratio, 1.63; 95% CI, 0.94-2.83; P=0.082). Cutoffs ranged widely across the included literature, and heterogeneity was substantial. These findings temper enthusiasm: NLR is biologically credible and consistently available, but a universal diagnostic threshold for SA-AKI is not justified.

NLR is affected by corticosteroids, catecholamine stress, bacterial or viral phenotype, hematologic disease, cancer therapy, chronic inflammation, and the timing of sampling. Absolute counts should be reviewed before interpreting the ratio because a similar NLR can arise from very different combinations of neutrophilia and lymphopenia. Serial change may be more clinically meaningful than a single number, particularly for prognosis, but prospective validation is needed.

Comparative and Combined Clinical Value

The three indices capture different domains and should not be treated as interchangeable. MDW reflects acute monocyte morphologic activation, RDW reflects erythrocyte heterogeneity shaped by both chronic and acute processes, and NLR reflects the balance between innate-cell expansion and adaptive-cell depletion.

Table 1. Comparative and Combined Clinical Value [27]

Index	Main biological signal	Principal strength	Major confounders	Most credible current role
MDW	Monocyte size heterogeneity during activation	Early sepsis-related signal generated with a compatible CBC analyzer	Analyzer platform, tube type, processing delay, monocyte disorders, immunosuppression	Addition to early ED sepsis and SA-AKI risk models
RDW	Anisocytosis related to inflammation, oxidative stress, and disordered erythropoiesis	Near-universal availability and low cost	Anemia, nutrient deficiency, transfusion, hemolysis, CKD, age, marrow disease	Contextual vulnerability and prognostic marker
NLR	Neutrophilia relative to lymphopenia	Simple calculation and potential value of serial change	Steroids, stress hormones, infection phenotype, malignancy, leukopenia	Early risk stratification and prognosis after SA-AKI

Pan et al. [27] provide the clearest head-to-head evidence. The AUCs of the MDW, RDW, and NLR models were 0.728, 0.712, and 0.719, respectively, when each index was combined with SOFA and MAP. The similarity of these estimates suggests that the clinical variables carried important information and that none of the hematologic markers dominated. The study did not establish that combining all three indices is superior to using one, nor did it validate a treatment threshold. A later case-control study by Lendak et al. [35] reinforced the potential importance of inflammatory parameters in SA-AKI, but current evidence remains insufficient to define a universal CBC-based score.



These observations support three principles. First, CBC indices should be added to a clinical model rather than interpreted alone. Second, trends may be more useful than fixed cutoffs because sepsis biology changes rapidly. Third, the intended use must be explicit. A tool designed to screen for sepsis, predict incident AKI, identify stage progression, or estimate mortality requires different timing, reference standards, and performance targets.

Integration With Kidney Assessment and Emerging Biomarkers

A practical SA-AKI assessment begins with the probability of sepsis, baseline renal reserve, and exposure to competing insults. CBC-derived signals can then modify risk but should not determine the diagnosis. A high-risk pattern might include rising MDW or NLR, elevated RDW, increasing SOFA score, falling MAP, oliguria, a small creatinine increase, lactate elevation, or exposure to nephrotoxic medication. The response should be closer assessment, not automatic labeling.

A clinically defensible workflow is: Confirm suspected or established sepsis using infection evidence, organ dysfunction, and serial clinical assessment. Establish the best available baseline creatinine and begin accurate hourly urine-output monitoring in patients at risk. Review MDW, RDW, NLR, absolute leukocyte counts, hemoglobin indices, and relevant prior CBC values. Reassess perfusion, volume status, venous congestion, MAP, lactate, and vasopressor requirements. Exclude or address alternative renal insults, including obstruction, nephrotoxins, contrast exposure, rhabdomyolysis, glomerular disease, and abdominal compartment physiology. Repeat creatinine, urine output, and selected hematologic indices according to clinical trajectory. Consider cystatin C, NGAL, or urinary TIMP-2·IGFBP7 when available and when the result will change monitoring or management.

This framework preserves the KDIGO diagnosis while using CBC indices to influence surveillance intensity. Biomarkers are most useful when they lead to a defined action. In a patient with a concerning hematologic profile but normal creatinine, appropriate actions may include more reliable urine measurement, avoidance of unnecessary nephrotoxins, dose review, hemodynamic reassessment, and earlier repeat testing. They do not include withholding necessary antimicrobials, indiscriminate fluid administration, or initiating kidney replacement therapy solely because a ratio is elevated.

Biomarker interpretation also depends on pretest probability. A mildly abnormal NLR or RDW in an older patient with anemia and chronic kidney disease has limited specificity. A rapidly rising MDW or NLR in a patient with infection, worsening hypotension, and declining urine output is more concerning. Combining routine markers with kidney-specific stress or damage biomarkers may improve phenotyping, but published biomarker studies show that performance changes with timing and AKI stage [17-21]. Bedside use therefore requires clear questions and an appreciation of false-positive and false-negative results [36].

Limitations of the Evidence and Research Priorities

The evidence base has several weaknesses. Much of the SA-AKI literature is retrospective and single-center. Sepsis-2, Sepsis-3, SOFA-based definitions, and variable infection criteria have been used across studies. AKI definitions, baseline creatinine estimation, urine-output capture, and temporal attribution also differ. These variations create spectrum bias and make threshold comparison unreliable [3,6].

Confounding is substantial. MDW, RDW, and NLR rise with illness severity and may predict general organ dysfunction rather than renal injury specifically. Anemia, transfusion, hematologic disease, malignancy, corticosteroids, chronic inflammatory disorders, pre-existing kidney disease, and laboratory platform differences are not uniformly controlled. Model performance may be optimistic when variable selection and validation occur in the same dataset. Many studies report association or AUC without calibration, decision-curve analysis, reclassification, or comparison against a parsimonious clinical model.

Future studies should use prospective multicenter cohorts, Sepsis-3, KDIGO criteria including urine output, and the consensus temporal framework for SA-AKI [3]. Baseline kidney function and competing causes of AKI should be adjudicated. Sampling should be standardized at presentation and repeated at clinically meaningful intervals. Models should compare: clinical variables alone; each CBC index added separately; all three indices together; and CBC indices plus kidney-specific biomarkers. External



validation should report discrimination, calibration, sensitivity, specificity, predictive values across risk strata, and net clinical benefit.

Dynamic phenotyping deserves particular attention. Serial NLR already appears more informative for prognosis than an isolated measurement [33], while the value of repeated MDW and RDW for incident SA-AKI remains uncertain. Machine-learning models may accommodate nonlinear interactions and trajectories, but they require transparent feature handling, reliable missing-data methods, and validation across health systems [37,38]. Simpler scores may ultimately be more transportable in emergency departments and resource-limited settings. Regardless of the prediction method, management should remain anchored in established sepsis and SA-AKI treatment principles rather than biomarker normalization alone [40].

The decisive question is not whether these indices are statistically associated with SA-AKI, but whether their use changes care and improves patient-centered outcomes. Pragmatic trials or implementation studies should test whether CBC-guided alerts shorten recognition time, reduce nephrotoxin exposure, improve urine-output monitoring, or reduce severe and persistent AKI without producing alarm fatigue or unnecessary intervention. Research priorities in sepsis and AKI increasingly emphasize biologic heterogeneity, standardized endpoints, and clinically actionable tools [38,39].

Conclusion

MDW, RDW, and NLR provide rapid, inexpensive information about the host response to sepsis and can assist early recognition of patients at risk for SA-AKI. Their biological signals are complementary, but none is sufficiently kidney specific or consistently accurate to diagnose SA-AKI alone. The most relevant evidence shows moderate discrimination when each marker is combined with SOFA score and MAP, supporting integrated risk assessment rather than isolated cutoffs. MDW may be particularly useful as an early monocyte-activation signal where compatible analyzers are available, RDW provides broader information about inflammatory and hematologic vulnerability, and NLR offers accessible risk stratification with potential additional value from serial change. For current practice, these indices should prompt closer kidney surveillance and review of reversible insults while KDIGO criteria remain the diagnostic standard. Prospective multicenter validation is required before a universal CBC-based prediction score can guide treatment.



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