Diagnostic Accuracy of Serum and Urinary Neutrophil Gelatinase-associated Lipocalin for Predicting Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

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Introduction. Sepsis-associated acute kidney injury (SA-AKI) is a frequent and serious complication among critically ill patients and is associated with substantial morbidity and mortality. Conventional diagnostic markers such as serum creatinine and urine output often detect kidney injury only after functional decline and may be confounded in septic states. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a potential early biomarker of tubular injury; however, its diagnostic performance in sepsis remains uncertain. This systematic review and meta-analysis evaluated the diagnostic accuracy of serum and urinary NGAL for predicting SA-AKI in adults with sepsis.

Methods. A systematic search of the PubMed database was conducted from inception to 2025 to identify studies evaluating serum, plasma, or urinary NGAL in adult patients with sepsis. Eligible studies reported diagnostic accuracy for AKI defined according to KDIGO, AKIN, or RIFLE criteria. Data extraction was performed independently by two reviewers. Pooled sensitivity, specificity, diagnostic odds ratios (DORs), and summary receiver operating characteristic (SROC) curves were estimated using a bivariate random-effects model. Subgroup analyses explored differences according to clinical setting and timing of biomarker measurement.

Results. Seventeen studies met the inclusion criteria. For serum NGAL, the pooled sensitivity was 0.77 (95% CI: 0.63 to 0.86) and pooled specificity was 0.68 (95% CI: 0.52 to 0.80), with an AUC of 0.773 and a diagnostic odds ratio of 6.15 (95% CI: 4.38 to 8.64). Urinary NGAL demonstrated comparable but slightly higher diagnostic performance, with pooled sensitivity of 0.75 (95% CI: 0.66 to 0.82), specificity of 0.71 (95% CI: 0.64 to 0.78), an AUC of 0.782, and a diagnostic odds ratio of 7.12 (95% CI: 4.17 to 12.16). Subgroup analyses suggested modestly improved diagnostic performance in ICU populations.

Conclusions. Both serum and urinary NGAL demonstrate moderate diagnostic accuracy for predicting SA-AKI in adult patients with sepsis. Urinary NGAL showed slightly better discriminatory performance in several clinical contexts. Rather than replacing established KDIGO-based diagnostic criteria, NGAL may serve as a complementary biomarker to support early risk stratification. Larger prospective studies with standardized assay methods and diagnostic thresholds are needed before routine clinical implementation.

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection and continues to represent a major cause of morbidity and mortality worldwide.[1] Among the complications associated with sepsis, acute kidney injury (AKI) is particularly common and clinically significant. It occurs in approximately 30 to 50% of critically ill septic patients and is associated with prolonged hospitalization, increased need for renal replacement therapy, and a higher risk of death.[2-4] Sepsis-associated acute kidney injury (SA-AKI) arises through a complex interplay of mechanisms, including microvascular alterations, inflammatory responses, oxidative stress, mitochondrial dysfunction, and apoptosis of tubular epithelial cells.[5-7]

In clinical practice, AKI is typically diagnosed using changes in serum creatinine levels and urine output according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[8] These markers, however, have important limitations. Serum creatinine is an indirect indicator of renal function and often rises only after substantial kidney injury has already occurred, sometimes 24 to 48 hours later.[9] In addition, creatinine levels can be influenced by several factors such as age, muscle mass, fluid balance, and hemodynamic instability—conditions frequently present in patients with sepsis.[10] Because of these limitations, there has been growing interest in identifying biomarkers including cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase 2, and insulin-like growth factor–binding protein 7 that can signal kidney injury earlier in the disease process.

One candidate that has received considerable attention is neutrophil gelatinase-associated lipocalin, also referred to as lipocalin-2.[11] NGAL is a 25-kDa protein belonging to the lipocalin family and is rapidly produced and expressed by neutrophils and various epithelial cells, including renal tubular epithelial cells following ischemic or inflammatory injury.[12,13] Both plasma and urinary NGAL concentrations can increase within a few hours of kidney injury, often before detectable changes occur in serum creatinine.[14,15] Experimental studies further suggest that NGAL expression reflects tubular stress and inflammatory activation, which are central components of the pathophysiology of SA-AKI.[5,16]

A number of clinical investigations have evaluated NGAL as a predictor of AKI in different settings, including cardiac surgery, critical care, and emergency department populations.[17-9] Nevertheless, its diagnostic value in patients with sepsis remains uncertain. Because sepsis is characterized by systemic inflammation and neutrophil activation, circulating NGAL levels may increase even in the absence of kidney injury, potentially reducing diagnostic specificity.[20,21] In addition, differences among studies—including assay methods, cutoff thresholds, timing of biomarker measurement, definitions of AKI (RIFLE, AKIN, or KDIGO), and study design—have contributed to substantial variability in reported diagnostic performance.[22,23]

Another unresolved question is whether NGAL measured in serum or plasma performs differently from NGAL measured in urine in this setting. Circulating NGAL can originate not only from the kidneys but also from other tissues during systemic inflammation, whereas urinary NGAL is generally thought to more closely reflect tubular injury.[24,25] In addition, NGAL has a relatively small molecular weight (~25 kDa), which means it can pass through the glomerular filtration barrier. Under normal conditions, filtered NGAL is largely reabsorbed and degraded by proximal tubular cells, but changes in glomerular filtration or tubular function may alter urinary NGAL levels and complicate its interpretation as a marker of intrinsic tubular damage.[13,26] The diagnostic performance of NGAL may also depend on the clinical context, such as whether patients are evaluated in the intensive care unit or the emergency department, as well as the timing of biomarker measurement during the course of sepsis.[27,28] Furthermore, the source of sepsis itself may influence NGAL levels. For instance, sepsis caused by urinary tract infection or pyelonephritis—conditions that may already involve renal injury—could produce different NGAL patterns compared with sepsis originating from non-renal sources such as skin, pulmonary, or intra-abdominal infections. Taken together, these factors highlight the need for a comprehensive synthesis of the available evidence.

In light of these considerations, we conducted a systematic review and bivariate random-effects meta-analysis to evaluate the diagnostic accuracy of serum and urinary NGAL for predicting sepsis-associated acute kidney injury in adult patients. Subgroup analyses were also performed according to clinical setting to explore potential sources of heterogeneity.

MATERIALS AND METHODS

Study Design and Reporting Standards

This systematic review and diagnostic meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. The aim of the study was to assess the diagnostic performance of serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) for predicting sepsis-associated acute kidney injury (SA-AKI) in adult patients.

Search Strategy

A systematic search of the PubMed database was conducted from inception through 2025. The following Boolean search strategy was applied:

("Neutrophil Gelatinase-Associated Lipocalin"[Mesh] OR "neutrophil gelatinase-associated lipocalin"[Title/Abstract] OR NGAL[Title/Abstract] OR "lipocalin-2"[Title/Abstract]) AND ("Sepsis"[Mesh] OR sepsis[Title/Abstract] OR septic[Title/Abstract] OR "septic shock"[Title/Abstract]) AND ("Acute Kidney Injury"[Mesh] OR "acute kidney injury"[Title/Abstract] OR AKI[Title/Abstract]) NOT (review[Publication Type] OR meta-analysis[Publication Type]) NOT ("cardiac surgery"[Title/Abstract] OR "cardiopulmonary bypass"[Title/Abstract] OR transplant[Title/Abstract]) AND (predict* OR prognos* OR associat* OR "risk factor*" OR ROC OR AUC OR odds OR hazard)*

The search excluded review articles, meta-analyses, cardiac surgery populations, cardiopulmonary bypass studies, and transplant-related studies to focus specifically on sepsis-associated AKI in medical populations. Reference lists of eligible studies were also screened to identify additional relevant articles.

Eligibility Criteria

Studies were included if they:

1. Included adult patients diagnosed with sepsis or septic shock.
2. Evaluated serum, plasma, or urinary NGAL.
3. Assessed NGAL for prediction or diagnosis of acute kidney injury.
4. Reported sufficient data to construct 2×2 contingency tables (TP, FP, FN, TN).
5. Used recognized AKI definitions (KDIGO, AKIN, or RIFLE).

Studies were excluded if they:

1. Were non-human or mechanistic studies.
2. Included pediatric or neonatal populations.
3. Did not evaluate NGAL as a diagnostic test for AKI.
4. Focused exclusively on mortality, chronic kidney disease progression, or non-AKI outcomes.
5. Were reviews, editorials, bibliometric studies, or conference abstracts without extractable data.
6. Lacked sufficient diagnostic accuracy information.

Study Selection

Titles and abstracts were first screened to remove clearly irrelevant records. Full-text versions of potentially eligible articles were then reviewed in detail against the predefined inclusion criteria. Although the review protocol was not prospectively registered, the eligibility criteria, outcomes of interest, and statistical methods were defined before data extraction began. Two reviewers independently screened the titles and abstracts of retrieved articles to identify potentially relevant studies. Full-text articles were then evaluated according to the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus, and when necessary, a third reviewer was consulted to reach a final decision.

Data Extraction

Data extraction was performed independently using a standardized collection form. The following information was recorded for each study: first author, year of publication, country, study design, and clinical setting. Additional data included total sample size, diagnostic criteria used for sepsis and AKI, type of NGAL measured (serum/plasma or

urine), and the reported NGAL cutoff value. Across the included studies, the diagnostic criteria used to define sepsis varied and included Sepsis-3, Surviving Sepsis Campaign criteria, ACCP/SCCM definitions, and earlier consensus frameworks. Definitions of acute kidney injury were primarily based on KDIGO criteria, although some earlier studies applied AKIN or RIFLE classifications.

Serum and plasma NGAL measurements were analyzed together under the category of "serum NGAL," as these matrices have comparable analytical characteristics and are frequently used interchangeably in clinical studies. When multiple NGAL cutoff values were reported, the threshold identified by the study authors as the optimal diagnostic cutoff—typically based on receiver operating characteristic (ROC) analysis or Youden's index—was selected. If measurements were reported at multiple time points, the earliest clinically relevant value used for AKI prediction was extracted to ensure consistency across studies.

Diagnostic accuracy data were collected as true positives, false positives, false negatives, and true negatives. When these values were not directly reported, 2 × 2 contingency tables were reconstructed from the available sensitivity, specificity, and sample size information whenever possible.

Quality Assessment

The methodological quality of included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This framework assesses potential risk of bias across four domains: patient selection, index test, reference standard, and flow and timing. In addition, concerns regarding the applicability of each study to the review question were considered. Each domain was judged as having low, high, or unclear risk of bias based on predefined signaling questions.

Statistical Analysis

All statistical analyses were performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria). Diagnostic meta-analyses were conducted using the mada and metafor packages. A bivariate random-effects model was used to jointly estimate pooled sensitivity and specificity while accounting for the correlation between these measures and potential heterogeneity among studies. Summary receiver operating characteristic (SROC) curves were constructed, and the area under the curve (AUC) was calculated to summarize overall diagnostic performance. The pooled diagnostic odds ratio (DOR) with 95% confidence intervals was also estimated using a random-effects model. Between-study heterogeneity was assessed using the Zhou and Dendukuri I^2 statistic, which extends conventional heterogeneity measures to bivariate diagnostic test accuracy models and incorporates the correlation between sensitivity and specificity.

Subgroup and Sensitivity Analyses

Prespecified subgroup analyses were conducted according to:

- Clinical setting (ICU vs. ED/ER)
- Leave-one-out sensitivity analyses were performed to evaluate the influence of individual studies on pooled estimates.

Publication Bias

Publication bias was assessed using Deeks' funnel plot asymmetry test. A P value < .10 was considered indicative of potential small-study effects.

RESULTS

Study Selection

The literature search identified 133 records in the PubMed database. No duplicate records were detected. After screening titles and abstracts, 101 studies were excluded for reasons such as non-human or mechanistic design, pediatric populations, absence of NGAL evaluation, non-sepsis cohorts, intervention studies, or lack of diagnostic accuracy outcomes. The remaining 32 articles underwent full-text review. Of these, 15 studies were excluded because they did not provide extractable diagnostic accuracy data, included mixed or non-sepsis populations, evaluated biomarker models without reporting standalone NGAL performance, or represented small pilot datasets with unstable estimates. Ultimately, 17 studies met the eligibility criteria and were included in the quantitative meta-analysis. The study selection process is summarized in Figure 1.

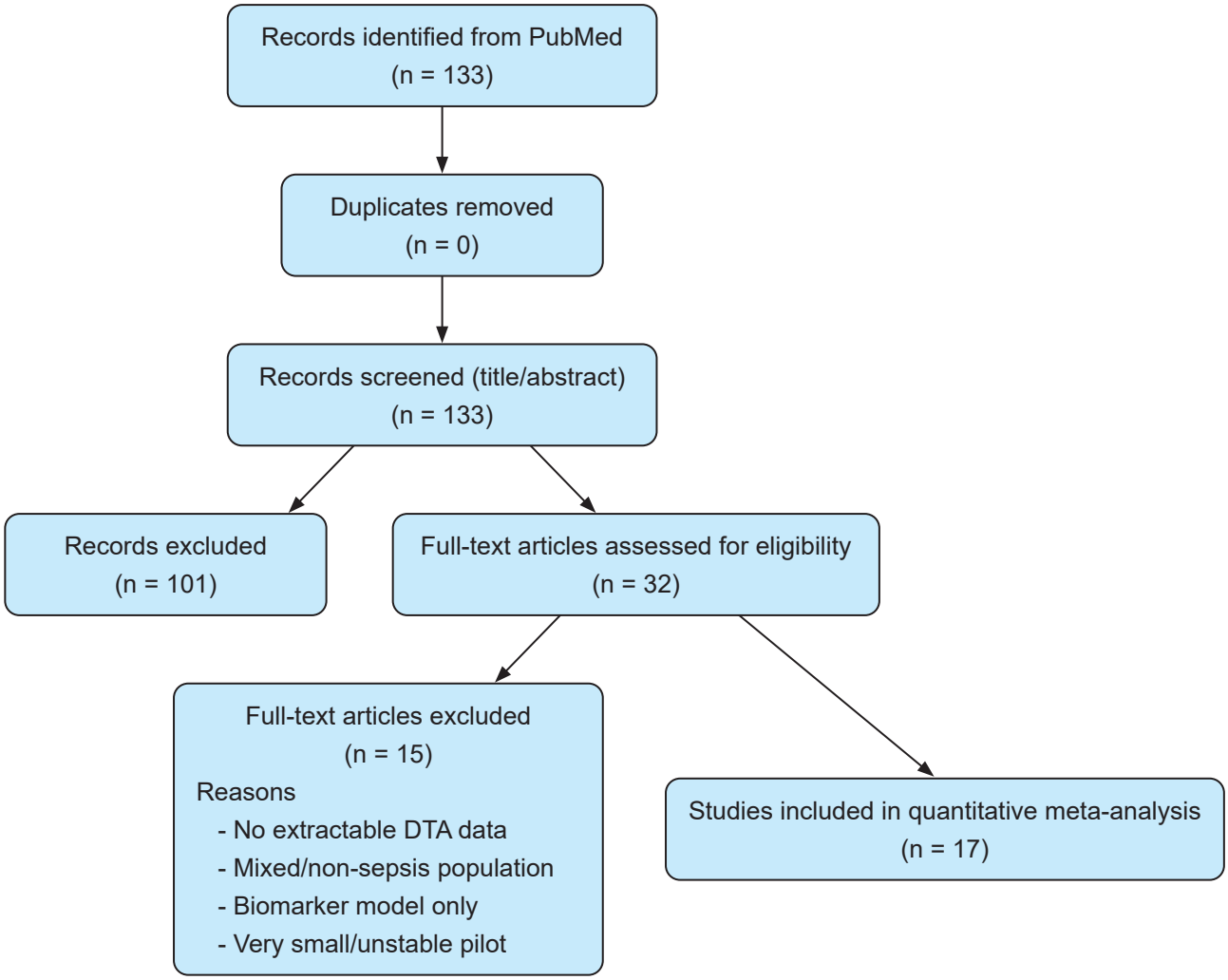


Figure 1. PRISMA flow diagram of the study selection process (A total of 133 records were identified through PubMed database searching. No duplicate records were found. After title and abstract screening, 101 records were excluded. Thirty-two full-text articles were assessed for eligibility, of which 15 were excluded for predefined reasons (no extractable diagnostic accuracy data, mixed/non-sepsis population, biomarker model only, or very small/unstable pilot studies). Ultimately, 17 studies met the inclusion criteria and were included in the quantitative meta-analysis)

Study Characteristics

A total of 17 studies published between 2010 and 2025 were included in the final analysis. These investigations were conducted across diverse geographic regions, including China, Korea, Brazil, Egypt, Malaysia, the Netherlands, Sweden, Turkey, the Czech Republic, Japan, and the United States. Most studies used a prospective design, although one retrospective study and one cross-sectional study were also included. The majority of studies were conducted in intensive care unit (ICU) settings, with several enrolling patients from emergency departments (ED) or emergency rooms (ER). Sample sizes varied substantially, ranging from 25 to 661 participants.

With respect to biomarker type, seven studies evaluated plasma NGAL, eight assessed urinary NGAL, and two reported both plasma and urine measurements. Studies reporting both sample types contributed separate datasets to the serum and urine analyses. NGAL cutoff values varied widely across studies, reflecting methodological heterogeneity. Detailed characteristics of the included studies are summarized in Table 1.

Diagnostic Accuracy of Serum NGAL

Nine datasets evaluating serum (plasma) NGAL were included in the pooled analysis. Using

Characteristics of the Studies Included in the Meta-analysis

Author	Year	Country	Design	Clinical Setting	Total Sample Size	AKI Cases	Non-AKI Cases	AKI Definition	Sepsis Definition	NGAL Type	Cut-off Value	Time of Measurement	Assay Method
Hu[40]	2022	China	Prospective	ICU	110	33	77	KDIGO	Sepsis-3	Urine	170 ng/mL	ICU admission, 24h, 48h, 72h (ROC at 24h)	Immunoturbidimetric assay (NORMAN-2 analyzer)
Klementa[41]	2024	Czech Republic	Prospective	ICU	46	31	15	KDIGO 2012	Sepsis-3	serum	290 ng/mL	Day 1, Day 7 (ROC at Day 1)	Immunoturbidimetric assay (BioPorto NGAL kit)
Kim[42]	2017	Korea	Retrospective registry study	ED/ICU	167	41	126	KDIGO	Surviving Sepsis 2012 / Sepsis-3 reclassified	Plasma	493 ng/mL	At enrollment (single timepoint)	Triage NGAL fluorescence immunoassay (Alere)
Nga[43]	2015	Brazil	Prospective	ER	168	121	47	AKIN	Surviving Sepsis 2012	Urine	3.36 ng/mg creatinine*	< 24 h after admission	ELISA
Zaitoun[44]	2024	Egypt	Prospective	ICU	166	100	66	KDIGO	Sepsis syndrome	Both	Serum = 250 ng/mL / Urine = 475 ng/mL	≤ 2 h after admission	ELISA (Bioassay Tech Lab)
Pei[45]	2022	China	Prospective	ED	162	60	102	KDIGO 2012	Sepsis-3	Serum	95.6 ng/mL	At admission (first time when sepsis diagnosed)	ELISA (Abcam kit)
Fan[46]	2014	China	Prospective	ICU	126	58	68	RIFLE	Sepsis consensus	Urine	402 ng/mL	Peak uNGAL during hospitalization	Polyclonal antibody-based radioimmunoassay (RIA)
Ralib[47]	2015	Malaysia	Prospective	ICU	129	67	62	KDIGO	ACCP/SCCM Sepsis	Plasma	454 ng/mL	Within 24 hours of ICU admission	ARCHITECT chemiluminescent microparticle immunoassay (CMIA)
Qiu[48]	2021	China	Prospective	ICU	90	44	46	KDIGO	Sepsis-3	Urine	181.71 ng/mL	At ICU admission	Legend Max™ ELISA kit (BioLegend)
de Geus[49]	2013	Netherlands	Prospective	ICU	75	50	25	AKIN	ACCP/SCCM	Plasma	304 ng/mL	ICU admission	Triage® immunoassay (Biosite/Alere)
Park[50]	2019	Korea	Retrospective	ED	85	19	66	KDIGO	Sepsis-3	Urine	359 ng/mL	At emergency department presentation	Chemiluminescent microparticle immunoassay (Abbott Architect analyzer)
Li[51]	2024	China	Prospective	ICU	80	40	40	KDIGO	Sepsis-3	Urine	155.19 ng/mL	12 h after admission	ELISA (Abcam kit)

Table continued

Author	Year	Country	Design	Clinical Setting	Total Sample Size	AKI Cases	Non-AKI Cases	AKI Definition	Sepsis Definition	NGAL Type	Cut-off Value	Time of Measurement	Assay Method
Teker[52]	2025	Türkiye	Cross-sectional	ICU	101	66	35	KDIGO	Sepsis-3	Serum	39.25 ng/mL	First day	Not reported
Martensson[53]	2010	Sweden	Prospective	ICU	25	18	7	RIFLE/ AKIN	ACCP/SCCM	Plasma & Urine	Plasma = 120 ng/mL / Urine = 68 ng/mL	Twice daily sampling starting at ICU admission	ELISA (BioPorto Diagnostics, Denmark)
Aydogdu[54]	2013	Turkey	Prospective	ICU	129	63	66	RIFLE	2001 Sepsis Definition	Urine	29.5 ng/mL	On admission	ELISA (Human Lipocalin-2/ NGAL ELISA BiovendorTM).
Shapiro[29]	2010	USA	Prospective multicenter	ED	661	24	637	Creatinine +0.5 mg/ dL	SIRS-based	Plasma	150 ng/mL	At ED presentation (time 0, before treatment)	Fluorescent point-of-care immunoassay (Triage NGAL Test; Biosite Diagnostics, San Diego CA)
Shimoyama[55]	2020	Japan	Prospective	ICU	44	20	24	KDIGO ≥ 1	Sepsis-3	Urine	438.5 ng/mL	Immediately after ICU entry (Day 1)	ARCHITECT uNGAL assay (Abbott Japan)

*The cutoff value “3.36 ng/mg creatinine” represents urine NGAL normalized to urine creatinine concentration (uNGAL/Cr ratio).
Note: The table summarizes the main characteristics of the 17 studies evaluating NGAL for the early detection of AKI in patients with sepsis. Reported variables include the first author and publication year, country, study design, clinical setting, total sample size, number of AKI and non-AKI patients, definitions used for AKI and sepsis, type of NGAL measured (serum/plasma or urine), diagnostic cut-off values (ng/mL), timing of biomarker measurement, and the assay methods used for NGAL determination.

random-effects meta-analysis models, the pooled sensitivity was 0.77 (95% CI: 0.63 to 0.86) and the pooled specificity was 0.68 (95% CI: 0.52 to 0.80) (Figure 2A and 2B).

The summary receiver operating characteristic (SROC) curve demonstrated an area under the curve (AUC) of 0.773 (Figure 3), indicating moderate diagnostic performance for predicting sepsis-associated acute kidney injury. The pooled diagnostic odds ratio (DOR) was 6.15 (95% CI: 4.38 to 8.64), indicating that patients who developed AKI had over six times higher odds of elevated serum NGAL levels compared with those who did not develop AKI.

Between-study heterogeneity was moderate according to the Zhou and Dendukuri I^2 statistic (I^2 = 43.2%), suggesting that a moderate proportion of the variability across studies reflects true differences rather than chance. Leave-one-out sensitivity analysis showed that removal of any individual study did not meaningfully change the pooled sensitivity, specificity, or DOR estimates

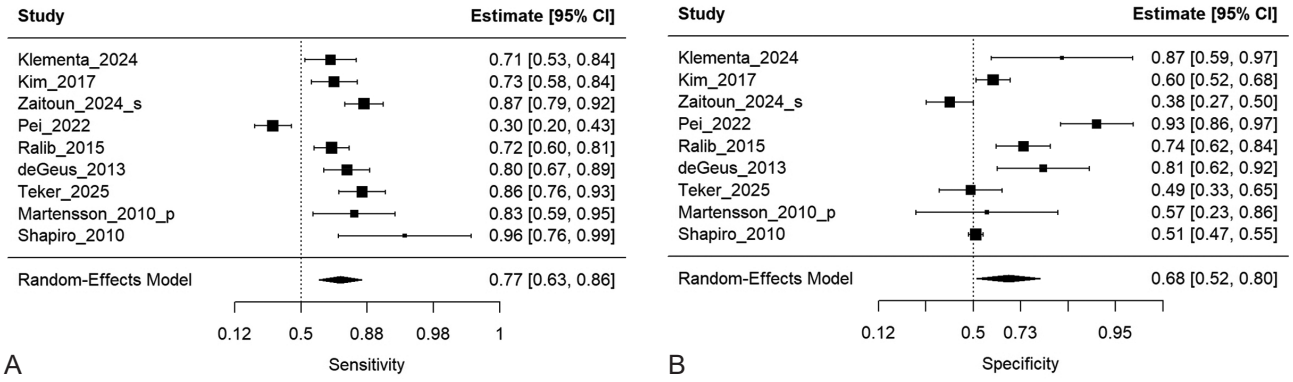


Figure 2. A) Forest Plot of Pooled Sensitivity for Serum/Plasma NGAL (Forest plot showing the sensitivity estimates of individual studies and the pooled sensitivity of serum/plasma NGAL for the detection of AKI in patients with sepsis. Each square represents the sensitivity estimate for an individual study, and the horizontal lines indicate the corresponding 95% confidence intervals (CIs). The size of the square reflects the relative study weight. The diamond represents the pooled sensitivity estimated using a bivariate random-effects model (pooled sensitivity = 0.77, 95% CI: 0.63 to 0.86)). B) Forest Plot of Pooled Specificity for Serum/Plasma NGAL (Forest plot showing the specificity estimates of individual studies and the pooled specificity of serum/plasma NGAL for the detection of AKI in patients with sepsis. Squares represent study-specific estimates, and horizontal lines indicate the corresponding 95% confidence intervals (CIs). The diamond represents the pooled specificity derived from the bivariate random-effects model (pooled specificity = 0.68, 95% CI: 0.52 to 0.80)).

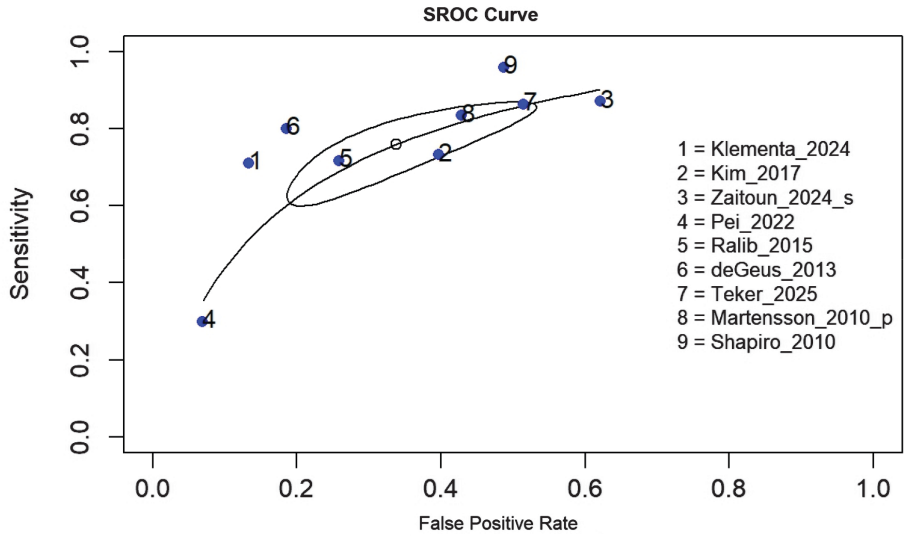
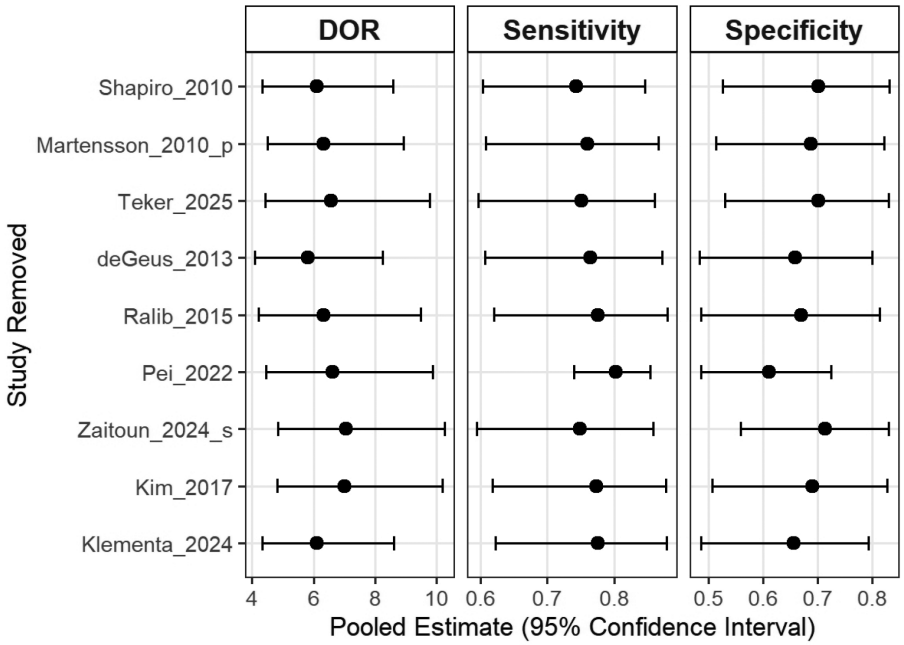


Figure 3. Summary ROC (SROC) Curve for Serum/Plasma NGAL (The SROC curve illustrates the overall diagnostic performance of serum/plasma NGAL for the detection of sepsis-associated AKI (Each point represents an individual study included in the meta-analysis. The solid curve represents the summary ROC estimated using the bivariate random-effects model, while the ellipse indicates the 95% confidence region around the summary operating point).



Supplementary Figure 1. Leave-one-out Analysis Showing the Change in Pooled Diagnostic Odds Ratio, Sensitivity, and Specificity After Sequential Removal of Each Individual Study (Excluding any single study did not materially alter the pooled estimates, indicating robust serum NGAL results).

(Supplementary Figure 1), indicating that the overall results were stable. The regression test for funnel plot asymmetry conducted on the serum/plasma NGAL studies indicated statistically significant evidence of potential publication bias (z = 2.03, P = .042). This suggests that small-study effects may have influenced the pooled diagnostic odds ratio for serum/plasma NGAL. The limit estimate of the intercept as the standard error approaches zero was 0.81 (95% CI: -0.24 to 1.87), indicating some degree of asymmetry in the funnel plot (Figure 4).

Diagnostic Accuracy of Urine NGAL

Ten datasets evaluating urinary NGAL were

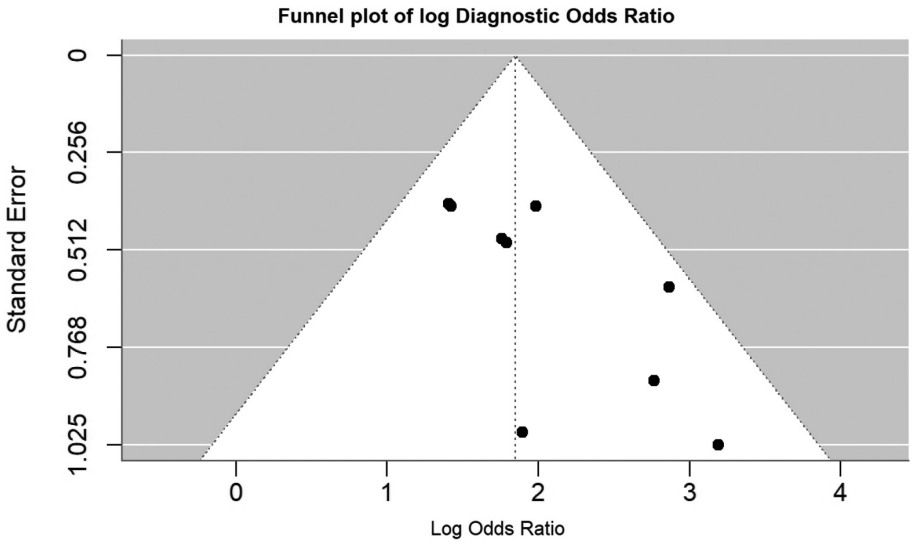


Figure 4. Funnel Plot of the Log Diagnostic Odds Ratio (DOR) Versus Standard Error for Studies Evaluating Serum/Plasma NGAL in Predicting Sepsis-associated AKI (Each point represents an individual study; the vertical dashed line indicates the pooled log DOR and the triangular region represents the expected 95% confidence limits. Deeks' regression test suggested significant funnel plot asymmetry (z = 2.03, P = .042), indicating potential publication bias.

included in the pooled analysis. The random-effects model yielded a pooled sensitivity of 0.75 (95% CI: 0.66 to 0.82) and a pooled specificity of 0.71 (95% CI: 0.64 to 0.78) (Figure 5A and 5B).

The SROC analysis produced an AUC of 0.782 (Figure 6), again indicating moderate diagnostic accuracy for predicting sepsis-associated acute kidney injury. The pooled diagnostic odds ratio (DOR) for urinary NGAL to predict acute kidney injury was 7.12 (95% CI: 4.17 to 12.16), suggesting that patients with AKI had over sevenfold higher odds of elevated urinary NGAL compared to those without AKI.

Between-study heterogeneity was low to moderate according to the Zhou and Dendukuri I^2 estimate (I^2 = 19.6%). Leave-one-out sensitivity analysis demonstrated that the pooled estimates remained stable when individual studies were excluded (Supplementary Figure 2). Regression test of funnel plot asymmetry for urine NGAL showed no statistically significant evidence of publication bias (z = 1.73, *P* = .08), suggesting the pooled diagnostic odds ratios are unlikely distorted by small-study effects (Figure 7).

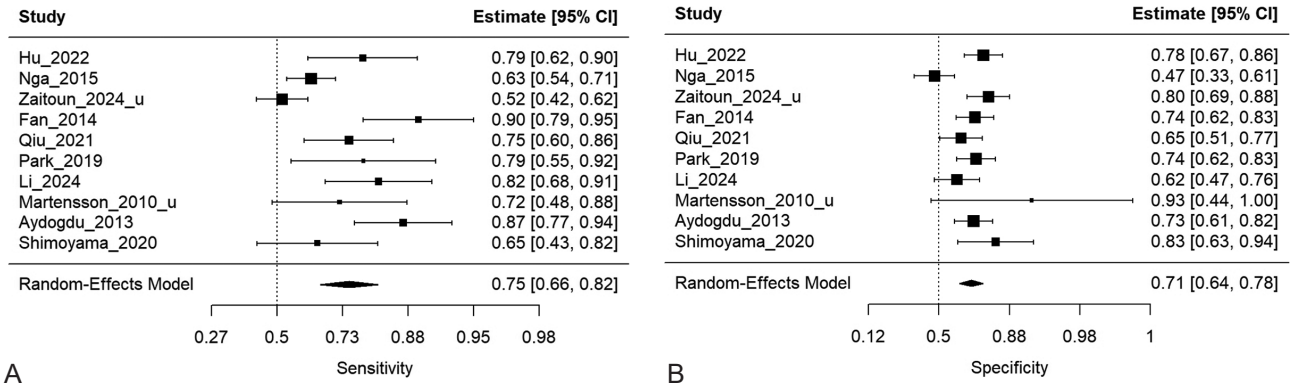


Figure 5. A) Forest plot displaying the sensitivity estimates of individual studies evaluating urinary NGAL for the detection of sepsis-associated AKI. Each square represents a study-specific estimate, with horizontal lines indicating 95% confidence intervals (CIs). Square size reflects the relative weight of each study. The diamond at the bottom depicts the pooled sensitivity derived from the bivariate random-effects model (pooled sensitivity = 0.75, 95% CI: 0.66 to 0.82). B) Forest plot showing the specificity estimates of individual studies assessing urinary NGAL for predicting sepsis-associated AKI. Study-specific estimates are shown as squares with 95% CIs indicated by horizontal bars. The size of each square corresponds to the study weight. The pooled specificity calculated using the bivariate random-effects model is shown as a diamond (pooled specificity = 0.71, 95% CI: 0.64 to 0.78).

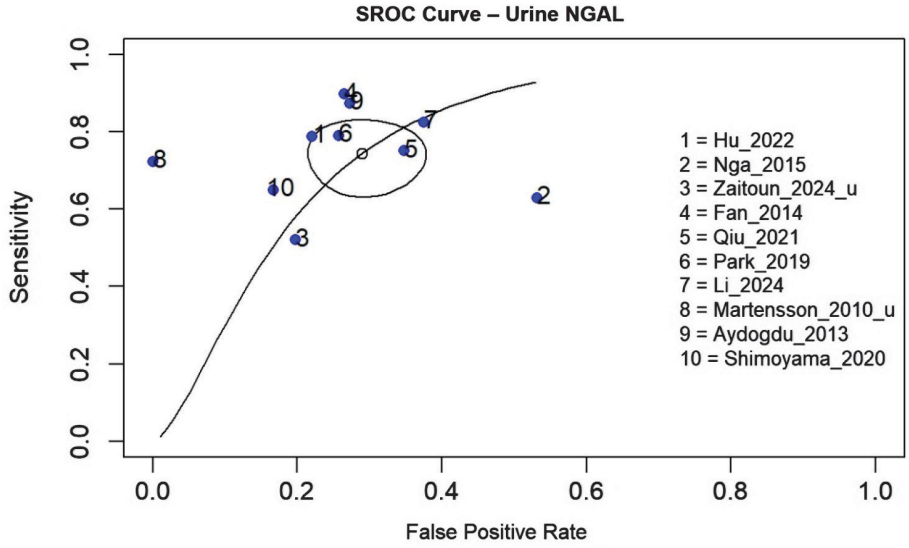
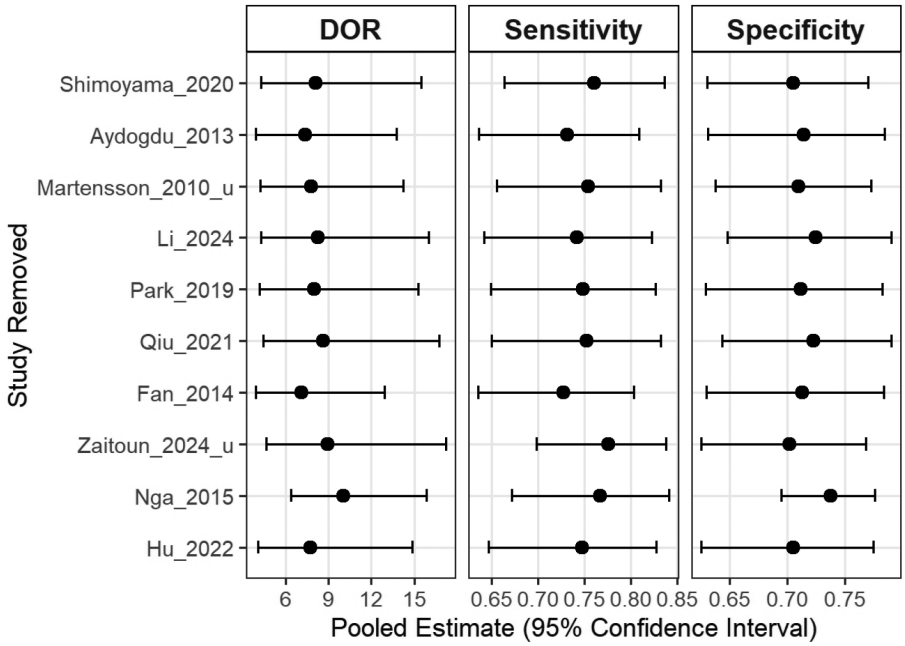


Figure 6. Summary ROC (SROC) Curve Depicting the Overall Diagnostic Performance of Urinary NGAL for Identifying Sepsis-associated AKI (Each point represents an individual study from the meta-analysis. The solid curve shows the summary ROC estimated using a bivariate random-effects model, and the ellipse indicates the 95% confidence region around the summary operating point).



Supplementary Figure 2. Leave-one-out Analysis Evaluating the Influence of Individual Studies on Pooled Urinary NGAL Diagnostic Performance (Sequential study exclusion produced minimal changes in sensitivity, specificity, and diagnostic odds ratio, demonstrating strong robustness of the urinary NGAL findings).

Subgroup Analyses

Clinical Setting.

Serum NGAL

In ICU populations (6 studies), serum NGAL demonstrated a pooled sensitivity of 0.80 (95% CI: 0.73 to 0.86) and a pooled specificity of 0.64 (95% CI: 0.46 to 0.79). The summary ROC curve showed an AUC of 0.81, indicating good diagnostic accuracy. Between-study heterogeneity was negligible (I^2 = 0In non-ICU settings (3 studies), including emergency department and mixed ED/ICU populations, serum NGAL demonstrated a

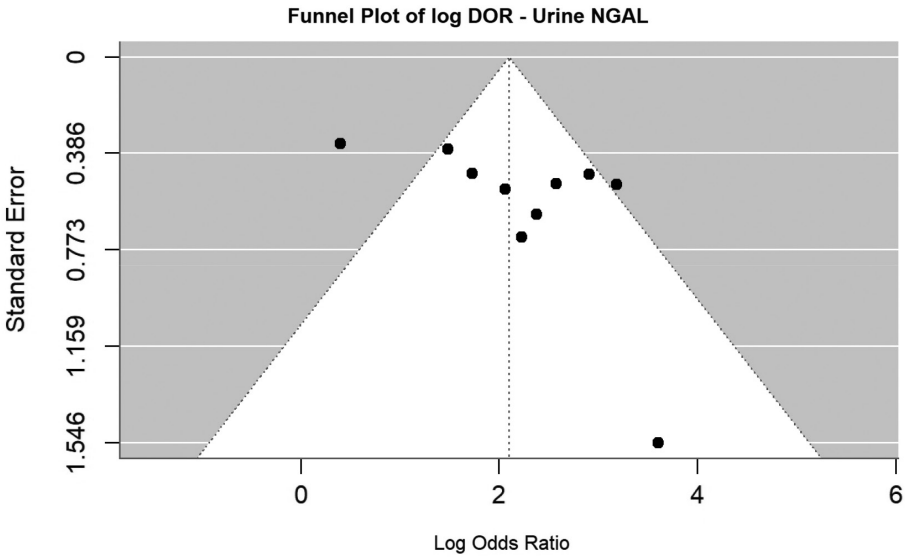


Figure 7. Funnel Plot of the Log Diagnostic Odds Ratio (DOR) Against Its Standard Error for Studies Evaluating Urinary NGAL in the Detection of Sepsis-associated AKI. Each point represents an individual study, with the vertical dashed line indicating the pooled log DOR and the triangular region representing the expected 95% confidence limits in the absence of publication bias. Visual inspection demonstrated no substantial asymmetry, and Deeks' regression test did not indicate statistically significant publication bias.

pooled sensitivity of 0.66 (95% CI: 0.28 to 0.90) and a pooled specificity of 0.73 (95% CI: 0.38 to 0.92). The summary ROC analysis yielded an AUC of 0.75, indicating moderate diagnostic accuracy. Between-study heterogeneity was minimal ($I^2 \approx 0\%$), although interpretation is limited by the small number of studies and wide confidence intervals

Urinary NGAL

In ICU populations (n = 8), urinary NGAL demonstrated a pooled sensitivity of 0.76 (95% CI: 0.65 to 0.84) and a pooled specificity of 0.74 (95% CI: 0.69 to 0.79). The summary ROC analysis yielded an AUC of 0.78, indicating moderate diagnostic accuracy. Between-study heterogeneity was low ($I^2 \approx 0\%$)."

In ED/ER settings (n = 2), urinary NGAL demonstrated a pooled sensitivity of 0.71 (95% CI: 0.51 to 0.85) and a pooled specificity of 0.62 (95% CI: 0.33 to 0.84), with an area under the curve (AUC) of 0.719. Due to the small number of included studies, these findings should be interpreted with caution.

DISCUSSION

In this systematic review and meta-analysis of adult patients with sepsis, both serum and urinary NGAL showed moderate accuracy for predicting sepsis-associated acute kidney injury (SA-AKI). Serum NGAL demonstrated a pooled sensitivity of 0.77 and specificity of 0.68, corresponding to an AUC of 0.773. Urinary NGAL showed slightly stronger overall diagnostic performance, with pooled sensitivity of 0.75, specificity of 0.71, and an AUC of 0.782. The pooled diagnostic odds ratio was also somewhat higher for urinary NGAL (7.12) than for serum NGAL (6.15), indicating modestly better overall performance. Subgroup analyses suggested that diagnostic performance was improved in ICU populations. Taken together, these findings support the concept that NGAL reflects evolving tubular stress and inflammatory injury during the progression of sepsis.

From a clinical standpoint, an AUC approaching 0.78 indicates that NGAL provides meaningful, though not definitive, diagnostic discrimination for early detection of SA-AKI. In practice, biomarkers with this level of performance are often most useful for early risk stratification rather than for establishing a definitive diagnosis. This may be particularly relevant in patients with evolving renal dysfunction, where serum creatinine changes often occur relatively late in the course of injury.

Our results are broadly consistent with prior large meta-analyses reporting moderate diagnostic performance of NGAL for AKI detection across diverse patient populations. Haase *et al.* reported pooled AUC values between 0.75 and 0.80 for NGAL among critically ill and surgical patients.[17] Bagshaw *et al.* observed higher NGAL concentrations in septic AKI compared with non-septic AKI, although overall diagnostic discrimination remained moderate.[20] Similarly, Shapiro *et al.* found that plasma NGAL provided moderate predictive value for AKI in emergency department patients with suspected sepsis.[29] The present analysis aligns with these findings, with pooled AUC values of 0.773 for serum NGAL and 0.782 for urinary NGAL, while incorporating more recent datasets and performing structured subgroup analyses.

The biological rationale for NGAL as an early biomarker of SA-AKI is well established. NGAL is released from renal tubular epithelial cells in response to ischemic and inflammatory injury and is also produced by activated neutrophils during systemic inflammation. In sepsis, microcirculatory disturbances, cytokine activation, and endothelial dysfunction can lead to early tubular stress before measurable changes in serum creatinine occur.[7] This pathophysiological sequence supports the potential value of NGAL as an early marker of kidney injury. At the same time, NGAL expression increases in systemic inflammatory states even in the absence of direct renal injury, which may limit specificity in septic populations.[30] This inflammatory confounding may partly explain the moderate specificity observed in the present pooled analyses, particularly for serum NGAL.

Sepsis-associated AKI remains strongly linked to increased morbidity and mortality.[1] Current KDIGO diagnostic criteria rely primarily on serum creatinine and urine output, both of which may lag behind the onset of structural kidney injury.[8] The findings of this study suggest that NGAL—particularly urinary NGAL—may serve as a useful

adjunct for early risk stratification in critically ill patients. However, the moderate specificity and variability in reported assay thresholds indicate that NGAL should not be used as a standalone diagnostic test. Instead, it is likely to be most informative when interpreted alongside clinical assessment and established diagnostic criteria.

Methodologically, this meta-analysis employed a bivariate random-effects model, which accounts for the inherent correlation between sensitivity and specificity and is widely recommended for diagnostic accuracy studies.[31,32] Reporting followed PRISMA-DTA guidance,[33,34] and risk-of-bias considerations were informed by QUADAS-2 principles.[35] Deeks' funnel plot asymmetry test suggested potential publication bias for serum NGAL (P = .042), whereas no statistically significant asymmetry was observed for urinary NGAL (P = .08). However, diagnostic meta-analyses that include fewer than 20 studies have limited statistical power to detect publication bias; therefore, these findings should be interpreted with caution.[36]

Across the included studies, reported NGAL cut-off values for predicting SA-AKI varied widely. Serum or plasma NGAL thresholds ranged approximately from 40 to nearly 500 ng/mL, while urinary NGAL cut-offs ranged from about 30 to over 400 ng/mL. This substantial variability likely reflects differences in assay platforms, timing of sample collection, patient populations, and AKI definitions across studies. Consequently, these values cannot be interpreted as universal diagnostic thresholds. In clinical practice, NGAL measurement may be most useful in several scenarios, including septic ICU patients with early oliguria, cases in which creatinine kinetics are unclear, and situations where rapid AKI risk stratification is required. Integration of NGAL measurements with KDIGO criteria or sepsis management bundles could potentially facilitate earlier nephrology consultation or more timely adjustment of fluid and vasopressor management.

An important consideration when evaluating novel biomarkers is whether earlier detection translates into improved clinical outcomes. Although NGAL has been shown to detect acute kidney injury several hours earlier than serum creatinine, current evidence mainly demonstrates improved diagnostic performance rather than clear reductions in mortality or long-term renal outcomes. Most studies evaluating NGAL have focused on diagnostic accuracy rather than biomarker-guided therapeutic interventions. Nevertheless, earlier identification of patients at risk for SA-AKI may facilitate closer hemodynamic monitoring, earlier nephrology consultation, and more timely adjustment of fluid management and nephrotoxic medications.[17,37,38]

Practical issues also influence the clinical applicability of NGAL testing. The cost of biomarker assays and the availability of standardized laboratory platforms may limit widespread implementation. In addition, variability among assay methods—including ELISA-based laboratory tests and automated immunoassays—can lead to differences in measured NGAL levels and reported diagnostic thresholds across studies. Although point-of-care NGAL assays have been developed and may provide faster results in emergency or intensive care settings, broader clinical adoption will likely depend on improved assay standardization, cost-effectiveness, and integration into routine laboratory workflows.[21,26,39]

LIMITATIONS

Several limitations should be considered when interpreting these findings. First, variability in the definitions of AKI (KDIGO, AKIN, and RIFLE) and sepsis (Sepsis-3 versus earlier criteria) may have introduced clinical heterogeneity across studies.[1,8] Second, NGAL cutoff values and assay platforms varied substantially among studies, potentially contributing to threshold effects. Third, subgroup analyses for emergency department settings and delayed-measurement cohorts were based on relatively small numbers of studies, which may limit the robustness of these estimates. Fourth, NGAL levels can increase in systemic inflammatory conditions independent of kidney injury, potentially reducing diagnostic specificity in septic populations.[30] Fifth, the literature search was primarily conducted in PubMed, and although reference lists were manually screened, relevant studies indexed exclusively in other databases such as Embase or Web of Science may have been missed. Finally, the wide variation in reported

diagnostic thresholds prevented the identification of a universally applicable NGAL cutoff value.

CONCLUSIONS

Both serum and urinary NGAL demonstrate moderate diagnostic accuracy for the prediction of sepsis-associated acute kidney injury. Urinary NGAL showed slightly better discriminatory performance than serum NGAL, particularly in ICU settings. However, given the variability in assay methods, diagnostic thresholds, and study populations, NGAL should be considered an adjunctive biomarker within established KDIGO-based diagnostic frameworks rather than a standalone diagnostic test. Further large-scale prospective studies using standardized assay platforms, consistent cutoff values, and clearly defined sampling time points are required to better define its clinical utility in the early detection of sepsis-associated AKI.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary materials and are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

Ilad Alavi Darazam and Amir Ahmad Nassiri serve as members of the RJCCN editorial team. The authors had no involvement in the peer-review or editorial decision-making processes for this manuscript.

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AUTHOR CONTRIBUTIONS

F.J.G. conceived the study, designed the protocol, performed data extraction, statistical analysis, and drafted the manuscript.

L.L. independently screened studies, verified extracted data, and contributed to interpretation of results.

A.A.N. Conceptualization, Supervision, Manuscript review

I.A.D. Conceptualization, Supervision, Manuscript review & editing and Correspondence with journal

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