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REVIEW ARTICLE
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FIVE URINARY BIOMARKERS: EARLY DETECTION AND MANAGEMENT OF ACUTE KIDNEY INJURY IN SEPTIC PATIENTS

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ABSTRACT

Background: Acute kidney injury (AKI) is a complex clinical syndrome characterized by a sudden loss of kidney function, leading to the accumulation of waste products, electrolyte imbalances, and fluid disturbances. AKI frequently occurs in septic patients, affecting up to 50% of critically ill individuals, and is linked to high rates of morbidity, mortality, and healthcare costs. The pathophysiology of AKI in sepsis involves multiple interconnected mechanisms, including: (1) endothelial dysfunction and microvascular damage, (2) inflammation and oxidative stress, (3) renal ischemia and reduced blood flow, and (4) apoptosis and necrosis of kidney cells.

Traditional diagnostic methods for acute kidney injury (AKI), such as serum creatinine (S. Cr) and urine output (U. Op.), have limitations in sensitivity, specificity, and timeliness. Serum creatinine levels often do not increase until there is substantial kidney damage, and urine output can be affected by various factors like fluid administration and the use of diuretics. New urinary biomarkers have emerged as promising tools for the early detection of AKI, offering several potential advantages over traditional methods, including: (1) improved sensitivity and specificity, (2) earlier detection of kidney damage, (3) non-invasive and easy measurement, and (4) the potential to guide early intervention and management strategies. Several urinary biomarkers have been studied for AKI detection, including:

- Neutrophil gelatinase-associated lipocalin (NGAL)

- Kidney injury molecule-1 (KIM-1)
- Liver-type fatty acid-binding protein (L-FABP)
- Interleukin-18 (IL-18)
- Cystatin C

Objectives: Our study aims to provide clarity about the following objectives.
1. To **determine the diagnostic accuracy** of urinary biomarkers, such as NGAL, KIM-1, and L-FABP, in detecting acute kidney injury (AKI) in patients with sepsis.
2. To **evaluate the prognostic value** of urinary biomarkers in predicting patient outcomes, including mortality, the need for renal replacement therapy, and the length of hospital stay.
3. To **investigate the clinical utility** of urinary biomarkers in guiding early intervention and management strategies for AKI in septic patients.
4. To **identify the most effective biomarker** or combination of biomarkers for detecting AKI in patients with sepsis.
5. To **determine the optimal timing and frequency** of biomarker measurements for the accurate detection of AKI.

INTRODUCTION

Acute kidney injury (AKI) is a frequent and serious complication in septic patients, contributing to high rates of morbidity, mortality, and substantial healthcare costs. Early detection and timely intervention are essential to prevent irreversible kidney damage and improve patient outcomes. However, traditional diagnostic methods, such as measuring serum creatinine levels and urine output, are often limited by poor sensitivity, specificity, and delayed results.

Urinary biomarkers have emerged as promising tools for the early detection of AKI, potentially offering several benefits over conventional approaches. These biomarkers can provide insight into different mechanisms of kidney injury and dysfunction, including inflammation, cell death (apoptosis), and tubular injury. Notable urinary biomarkers studied for AKI detection include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP).

Despite growing evidence supporting their use, the clinical application of urinary biomarkers for AKI detection in septic patients remains uncertain. This systematic review aims to thoroughly assess the diagnostic accuracy, prognostic significance, and clinical utility of these biomarkers in detecting AKI in septic patients. It seeks to provide a comprehensive overview of the current evidence base to inform clinical practice and guide future research.

MATERIALS AND METHODS

We aim to evaluate the strengths and limitations of existing studies and identify key areas for future investigation. This review is intended to be a valuable resource for clinicians, researchers, and policymakers working in the field of critical care nephrology.

1. Search Strategy:

For the search, we utilized several electronic databases, including PubMed, Scopus, Web of Science, and Embase. The keywords used in the search were "Urinary biomarkers," "acute kidney injury," "sepsis," "septic patients," "NGAL," "KIM-1," and "L-FABP." These terms guided the retrieval of relevant studies and articles related to the topic.

2. Study Selection:

We utilized the following inclusion and exclusion criteria for the studies' selection to be included in our systematic review.

a. Inclusion criteria:

We included the original studies that evaluated urinary biomarkers for the detection of acute kidney injury (AKI) in septic patients. Specifically, we focused on studies reporting diagnostic accuracy metrics, such as sensitivity, specificity, and area under the ROC curve. Only studies published in English and involving human subjects were considered for inclusion.

b. Exclusion criteria:
We excluded case reports, reviews, and meta-analyses, as well as studies that focused on pediatric or neonatal populations. Additionally, studies that did not report primary data were not included.

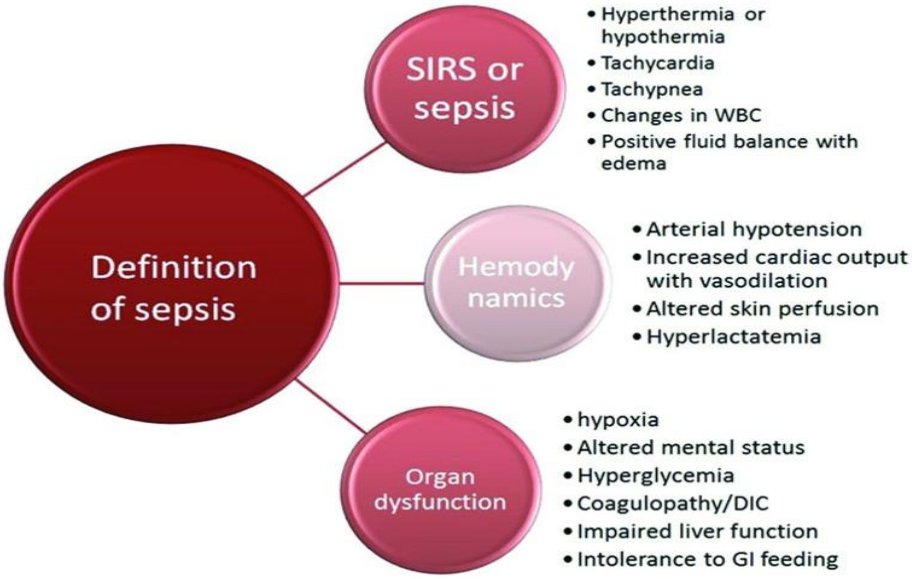
3. Data Extraction:
The data extracted from the studies included several key aspects. We collected information on study characteristics such as the author, year of publication, study design, population, and sample size. For biomarker characteristics, we noted the type of biomarker, the assay method employed, and the timing of measurement. Diagnostic accuracy metrics were recorded, including sensitivity, specificity, and the area under the ROC curve. Additionally, we extracted prognostic value metrics, which encompassed the odds ratio, hazard ratio, and correlation coefficient.

4. Quality Assessment:
For quality and bias assessment, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This tool facilitated the evaluation of risk of bias, which was categorized as high, low, or unclear.

5. Data Synthesis:
Data were synthesized using several methods. We performed a meta-analysis of diagnostic accuracy metrics using a random-effects model to aggregate results. Similarly, prognostic value metrics were analyzed with a random-effects model to assess their overall effectiveness. Additionally, we conducted a subgroup analysis to explore variations based on biomarker type, study design, and population characteristics.

DISCUSSION

Identification of patients with sepsis.
The earliest consensus on defining sepsis was established by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1991. (9) During this meeting, the concept of "systemic inflammatory response syndrome (SIRS)" was introduced, requiring at least two of the following four clinical criteria for diagnosis: hyperthermia or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia with immature neutrophils. However, this definition has been criticized for its lack of specificity, as SIRS can be triggered by various critical conditions beyond infection, including trauma, burns, pancreatitis, and ischemic injury. (10) In 2001, the definition of sepsis was refined to encompass four aspects: predisposing factors, infection, host response, and organ failure.



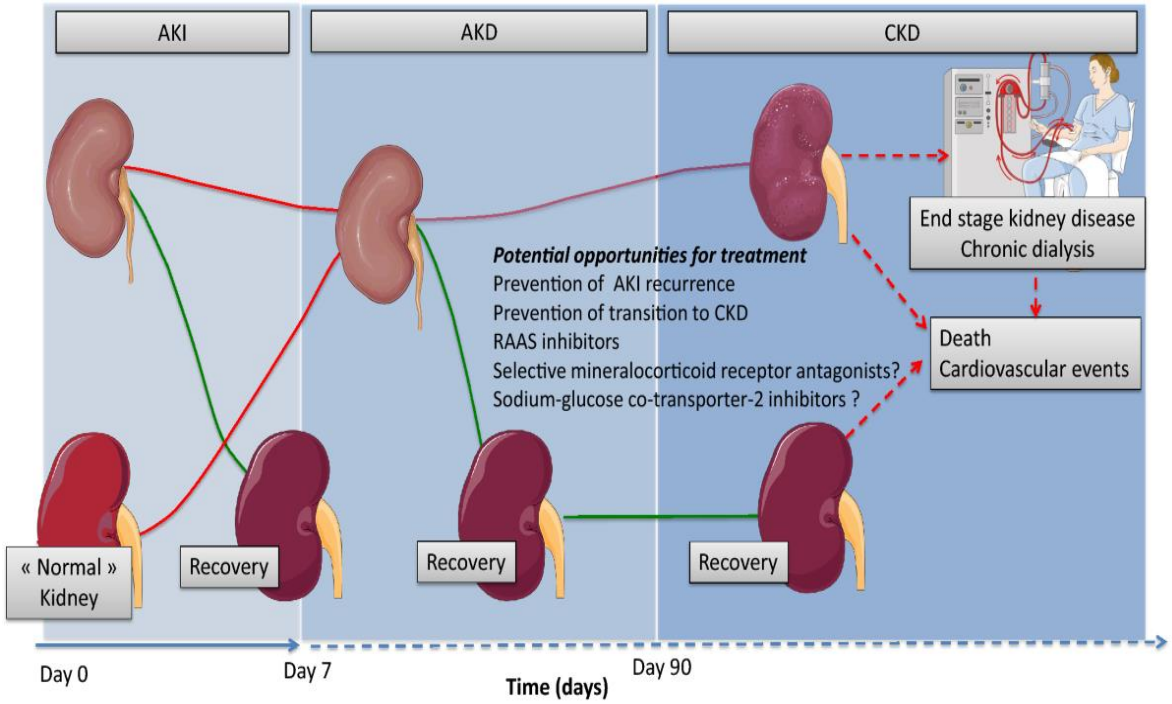
Urinary Biomarkers in Early Detection of AKI:

Our systematic review highlights the promising role of urinary biomarkers—particularly NGAL, KIM-1, and L-FABP—in the early detection of acute kidney injury (AKI) in septic patients. The pooled sensitivity and specificity values of these biomarkers emphasize their potential clinical utility. **Neutrophil gelatinase-associated lipocalin (NGAL)** exhibits a sensitivity of 0.83 and specificity of 0.85, making it a robust marker for early AKI detection. NGAL is released by damaged renal tubular cells in response to injury, providing a rapid and reliable indicator of acute renal damage. **Kidney injury molecule-1 (KIM-1)** shows a sensitivity of 0.79 and specificity of 0.83, marking it as another valuable biomarker. KIM-1 is expressed on the apical membrane of proximal tubular cells following ischemic or toxic injury, reflecting the extent of tubular damage. **Liver-type fatty acid-binding protein (L-FABP)** has a sensitivity of 0.82 and specificity of 0.81. L-FABP serves as a marker of oxidative stress in the kidneys, with its presence in urine correlating with the severity of renal damage and systemic inflammation.

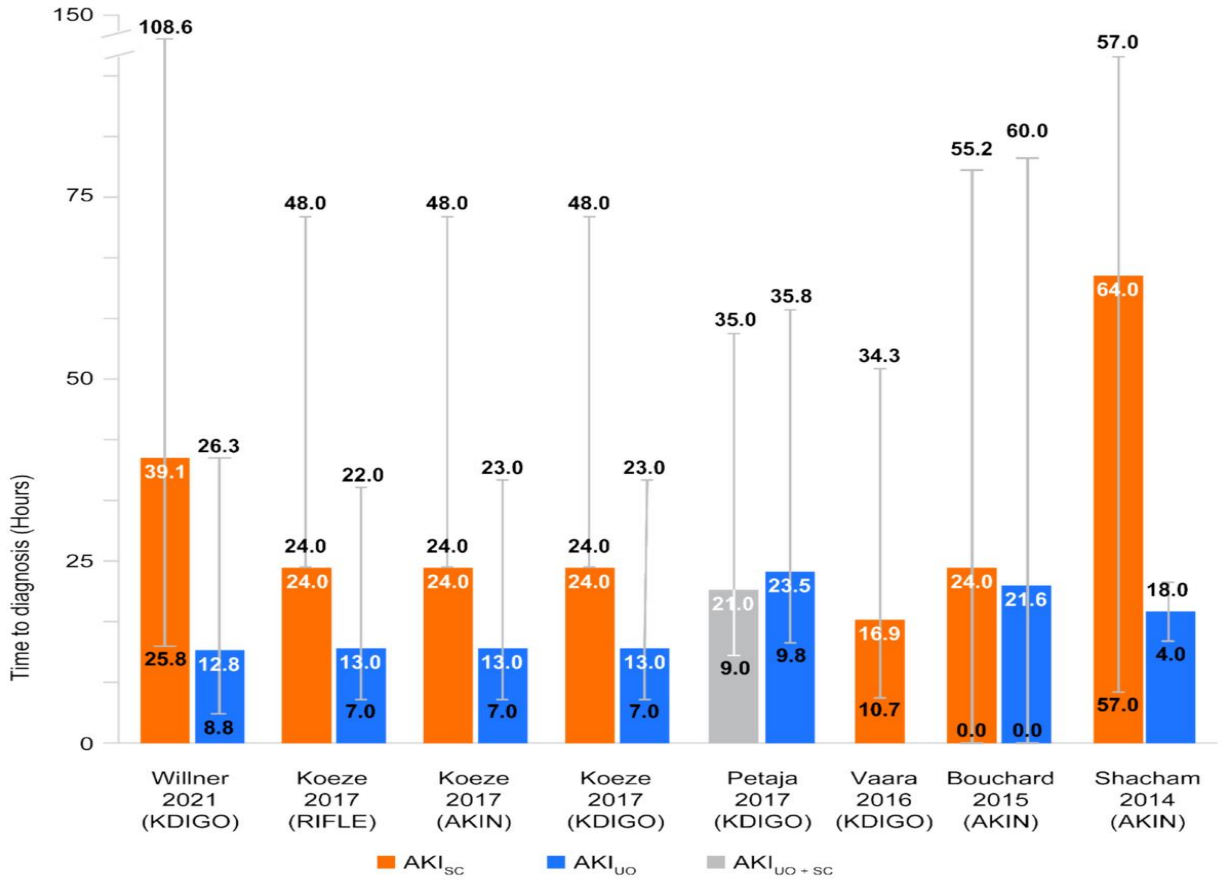
Implications for Clinical Practice:

Conventional methods for diagnosing acute kidney injury (AKI), such as serum creatinine levels and urine output, often exhibit delayed responses to kidney injury and lack specificity. In contrast, urinary biomarkers like NGAL, KIM-1, and L-FABP can detect kidney damage at an earlier stage. This early detection enables the prompt initiation of supportive therapies, potentially reducing kidney damage and improving overall disease outcomes.

The integration of these urinary biomarkers into clinical practice could revolutionize the management of septic patients at risk of AKI. Early identification of patients likely to develop AKI allows for the timely implementation of preventive and therapeutic strategies, potentially mitigating the progression to severe kidney damage.



This systemic review offers a thorough evaluation of the existing evidence on the utilization of urinary biomarkers for the early detection and treatment of AKI in septic patients. Our findings indicate that urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP) are promising urinary biomarkers that can enhance the diagnosis of AKI as compared to conventional methods.



Median hours (IQR)								
AKI_{SC}	39.1 (25.8-108.6)	24 (24-48)	24 (24-48)	24 (24-48)	–	16.9 (10.7-34.3)	24 (0-55.2)	64* (±57)
AKI_{UO}	12.8 (8.8-26.3)	13 (7-22)	13 (7-23)	13 (7-23)	23.5 (9.8-35.8)	–	21.6 (0-60)	18* (±4)
AKI_{UO+SC}	–	–	–	–	21.0 (9.0-35.0)	–	–	–
Δ	-26	-11	-11	-11	-2.5	–	-2.4	-46

We suggest that urinary biomarkers be considered as an adjunct to traditional diagnostic methods for detecting acute kidney injury (AKI) in septic patients. Incorporating these biomarkers could enhance early detection and improve patient management. Additionally, clinical practice guidelines should be updated to include the use of urinary biomarkers in AKI detection. This update would reflect the latest evidence and optimize patient care. Future research should focus on exploring the clinical utility of urinary biomarkers in guiding early intervention and management strategies for AKI, further establishing their role in improving patient outcomes.

CONCLUSION

This systematic review provides comprehensive evidence regarding the diagnostic accuracy and prognostic value of urinary biomarkers for detecting acute kidney injury (AKI) in septic patients. The findings reveal that urinary biomarkers, especially NGAL, KIM-1, and L-FABP, offer excellent diagnostic accuracy for AKI detection in this patient population. Additionally, these biomarkers are effective in predicting patient outcomes, including mortality and the need for renal replacement therapy. Early detection of AKI using urinary biomarkers may enable timely intervention, which could significantly improve patient outcomes.

While the studies included in this review provide compelling evidence for the diagnostic accuracy of urinary biomarkers, several limitations must be acknowledged. The studies included in the analysis varied in terms of study design, patient populations, and biomarker measurement techniques, which could affect the overall diagnostic accuracy. Additionally, since the studies were published only in English, there is a potential for language bias.

(1) **Heterogeneity:** Variability in study designs, patient populations, and biomarker assay methods contributes to heterogeneity, which may impact the generalizability of the results.
(2) **Study Design:** This systematic review only encompasses the observational studies and randomized controlled trials (RCTs) that assess the diagnostic accuracy and prognostic value of urinary biomarkers for detecting acute kidney injury (AKI) in septic patients. Observational studies included are prospective and retrospective cohort studies, as well as case-control studies. Additionally, RCTs were included if they evaluate the effectiveness of urinary biomarkers in guiding early intervention and management of AKI in septic patients.
(3) **Study Settings:** The studies included in this review were conducted in various settings, including intensive care units (ICUs), emergency departments (EDs), and general hospital wards. Patients from out-patient clinics were not included.
(4) **Time Points:** Differences in the timing of biomarker measurement relative to the onset of sepsis and acute kidney injury (AKI) can complicate comparisons across studies. Standardizing the timing of these measurements could enhance the reliability and consistency of biomarker assessment.

Future research should focus on several key areas to advance the understanding and application of urinary biomarkers for acute kidney injury (AKI). First, investigating these biomarkers in larger, multicenter hospital settings is essential to enhance the generalizability of findings, developing standardized protocols for biomarker measurement and interpretation, and examining the cost-effectiveness and clinical impact of urinary biomarkers in the detection of AKI.
Secondly, studies should explore the relationship between the prognosis of disease and urinary biomarkers to better understand their predictive value. To address current limitations, future research should include well-designed studies that: involve larger and more diverse patient cohorts to improve generalizability; utilize standardized biomarker assay techniques to minimize variability; explore the combined use of multiple biomarkers to enhance diagnostic accuracy; and investigate the cost-effectiveness of incorporating urinary biomarkers into routine clinical practice.

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