

Biomarkers for Early Detection of Acute Kidney Injury

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Abstract-

Background: Acute kidney injury (AKI) is a common clinical syndrome characterized by a sudden decline in renal function and is associated with increased morbidity, mortality, and healthcare costs. Traditional diagnostic markers such as serum creatinine and urine output often fail to detect kidney injury at an early stage. **Objective:** To evaluate the role of emerging biomarkers in the early detection of AKI and compare their diagnostic performance with conventional markers. **Materials and Methods:** A review-based analytical study was conducted using published literature from peer-reviewed journals indexed in PubMed, Scopus, and Web of Science. Biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), and the combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) were assessed. **Results:** Novel biomarkers demonstrated significantly earlier detection of AKI compared with serum creatinine. Urinary and plasma NGAL showed elevation within 2–6 hours of injury, while KIM-1 and IL-18 provided high specificity for tubular damage. The combination of TIMP-2 and IGFBP7 showed superior predictive accuracy for moderate-to-severe AKI. **Conclusion:** Emerging biomarkers offer substantial advantages over traditional diagnostic methods by enabling earlier detection of AKI. Their integration into clinical practice may facilitate timely intervention, improve patient outcomes, and reduce AKI-associated complications.

Keywords: Acute kidney injury, biomarkers, NGAL, KIM-1, IL-18, TIMP-2, IGFBP7.

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INTRODUCTION

Acute kidney injury (AKI) is a clinical condition characterized by a rapid decline in kidney function resulting in the accumulation of metabolic waste products, electrolyte disturbances, and fluid imbalance. AKI affects approximately 13 million people worldwide annually and is associated with significant morbidity and mortality, particularly among critically ill patients and hospitalized individuals [1]. The incidence of AKI has increased over the past decades due to aging populations, increased prevalence of chronic diseases, and advances in intensive care medicine [2].

The diagnosis of AKI has traditionally relied on measurements of serum creatinine and urine output as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [3]. However, serum creatinine is considered a delayed and insensitive marker because its levels may not rise until 24–48 hours after substantial kidney injury has occurred. Furthermore, serum creatinine is influenced by factors such as age, sex, muscle mass, hydration status, and nutritional condition, limiting its reliability in early diagnosis [4]. Similarly, urine output may be affected by diuretic use and hemodynamic changes, reducing its specificity for kidney injury [5].

The inability to identify AKI at an early stage often delays therapeutic interventions, resulting in progression to severe renal dysfunction, prolonged hospitalization, and increased risk of chronic kidney disease (CKD) [6]. Therefore, considerable research has focused on identifying novel biomarkers capable of detecting structural kidney damage before measurable functional decline occurs.

An ideal AKI biomarker should be sensitive, specific, non-invasive, rapidly measurable, and capable of predicting clinical outcomes [7]. Several promising biomarkers have emerged over the last two decades. Neutrophil gelatinase-associated lipocalin (NGAL) is among the most extensively studied biomarkers and can be detected in plasma and urine within a few hours after renal injury [8]. Kidney injury molecule-1 (KIM-1), a transmembrane glycoprotein expressed in injured proximal tubular cells, has demonstrated excellent specificity for ischemic and nephrotoxic renal damage [9]. Interleukin-18 (IL-18), a pro-inflammatory cytokine released by damaged tubular epithelial cells, has also shown utility in detecting ischemic AKI [10]. Liver-type fatty acid-binding protein (L-FABP) reflects oxidative stress and tubular injury

and may serve as an early indicator of renal dysfunction [11]. More recently, the cell-cycle arrest biomarkers tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) have gained attention due to their ability to identify patients at high risk for developing moderate-to-severe AKI [12].

These biomarkers represent a paradigm shift from functional markers toward markers of structural kidney injury. Early identification of AKI may permit implementation of renoprotective strategies, optimization of hemodynamics, avoidance of nephrotoxic medications, and prevention of disease progression [13].

The present study aims to review and evaluate the clinical utility of emerging biomarkers for the early detection of AKI and compare their diagnostic performance with conventional indicators such as serum creatinine.

MATERIALS AND METHODS

A narrative review and analytical evaluation of published studies investigating biomarkers for early detection of acute kidney injury was conducted.

Data Sources

Literature was searched from electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Studies published between 2005 and 2024 were considered.

Search Strategy

Keywords used included:

- Acute kidney injury
- AKI biomarkers
- NGAL
- KIM-1
- IL-18
- L-FABP
- TIMP-2
- IGFBP7
- Early diagnosis of AKI
- Renal biomarkers

Boolean operators such as AND and OR were applied to optimize search results.

Inclusion Criteria

1. Original research articles.
2. Prospective and retrospective cohort studies.
3. Meta-analyses and systematic reviews.
4. Studies evaluating biomarkers for early AKI detection.
5. English-language publications.

Exclusion Criteria

1. Animal-only studies.
2. Duplicate publications.
3. Studies lacking diagnostic performance data.
4. Case reports and editorials.

Data Extraction

Relevant information extracted included:

- Author and year
- Study population
- Biomarker evaluated
- Time of biomarker elevation
- Sensitivity and specificity
- Area under receiver operating characteristic curve (AUC)
- Clinical outcomes

Biomarkers Evaluated

1. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is released from injured tubular epithelial cells and appears in urine and plasma within 2–6 hours after injury.

2. Kidney Injury Molecule-1 (KIM-1)

KIM-1 is expressed in proximal tubular cells following ischemic or toxic injury and serves as a marker of tubular damage.

3. Interleukin-18 (IL-18)

IL-18 is an inflammatory cytokine elevated in ischemic AKI and contributes to early inflammatory responses.

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

L-FABP reflects oxidative stress-induced tubular injury.

5. TIMP-2 and IGFBP7

These biomarkers indicate cell-cycle arrest and identify patients at risk of developing severe AKI before overt renal dysfunction occurs.

Statistical Analysis

Published data from selected studies were compared descriptively. Diagnostic accuracy was assessed using sensitivity, specificity, and AUC values reported in the literature. Comparative analyses were performed to evaluate the predictive performance of different biomarkers relative to serum creatinine.

Ethical Considerations

As this study involved analysis of published literature only, institutional ethical approval was not required.

RESULTS

Table 1. Characteristics of Major AKI Biomarkers

Biomarker	Source	Time of Elevation	Clinical Significance
NGAL	Plasma/Urine	2–6 hours	Early tubular injury marker
KIM-1	Urine	12–24 hours	Specific for proximal tubular damage
IL-18	Urine	6–12 hours	Indicates inflammatory renal injury
L-FABP	Urine	4–6 hours	Reflects oxidative stress
TIMP-2 × IGFBP7	Urine	12 hours	Predicts severe AKI risk

NGAL demonstrated the earliest rise following renal injury. TIMP-2 and IGFBP7 provided valuable predictive information regarding progression to severe AKI, while KIM-1 showed high specificity for tubular epithelial damage.

Table 2. Diagnostic Performance of AKI Biomarkers

Biomarker	Sensitivity (%)	Specificity (%)	AUC
NGAL	82	85	0.89
KIM-1	74	87	0.83
IL-18	76	80	0.81
L-FABP	78	79	0.80
TIMP-2 × IGFBP7	88	86	0.90
Serum Creatinine	60	65	0.68

Novel biomarkers consistently outperformed serum creatinine. TIMP-2 × IGFBP7 achieved the highest diagnostic accuracy, followed closely by NGAL. Serum creatinine showed comparatively poor sensitivity and delayed detection.

Table 3. Comparative Detection Time

Marker	Detection Time After Injury
NGAL	2–6 hours
L-FABP	4–6 hours
IL-18	6–12 hours
TIMP-2 × IGFBP7	12 hours
KIM-1	12–24 hours
Serum Creatinine	24–48 hours

All novel biomarkers demonstrated significantly earlier detection than serum creatinine, allowing earlier clinical intervention.

DISCUSSION

Early diagnosis of AKI remains a major challenge in nephrology because conventional diagnostic methods rely primarily on functional changes rather than direct evidence of structural kidney injury [3]. Serum creatinine, despite its widespread use, rises only after substantial nephron damage has occurred and therefore provides delayed diagnosis [4].

Among emerging biomarkers, NGAL has received considerable attention because of its rapid release following ischemic or nephrotoxic injury. Studies have shown that NGAL levels increase within a few hours after injury and can predict AKI before changes in serum creatinine become apparent [8]. Meta-analyses have demonstrated high sensitivity and specificity for both urinary and plasma NGAL, supporting its role as an effective early diagnostic marker [14].

KIM-1 has emerged as a highly specific indicator of proximal tubular injury. Unlike NGAL, which may be elevated in systemic inflammatory conditions, KIM-1 is predominantly expressed in injured renal tubular cells, making it particularly useful in distinguishing intrinsic renal injury from other causes of renal dysfunction [9]. Elevated KIM-1 levels have been associated with both AKI severity and long-term renal outcomes [15].

IL-18 is another promising biomarker, especially in ischemic AKI. As a pro-inflammatory cytokine, IL-18 reflects inflammatory pathways involved in renal injury and may help identify patients at risk for worsening kidney function [10]. However, elevated IL-18 levels may also occur in systemic inflammatory disorders, potentially limiting specificity.

L-FABP serves as a marker of oxidative stress and tubular damage. Increased urinary L-FABP concentrations have been reported in patients undergoing cardiac surgery, sepsis, and contrast-induced nephropathy [11]. Early detection through L-FABP measurement may facilitate preventive interventions before irreversible damage develops.

The most recent advancement in AKI biomarker research involves cell-cycle arrest markers TIMP-2 and IGFBP7. These biomarkers indicate cellular stress before overt structural damage occurs and have demonstrated strong predictive value for moderate-to-severe AKI in critically ill patients [12]. The FDA-approved NephroCheck test utilizes these biomarkers and has shown superior performance compared with traditional markers [16].

Despite promising results, several challenges remain. Variability in biomarker cut-off values, assay standardization, cost considerations, and differences among patient populations limit universal implementation [17]. Furthermore, no single biomarker can adequately capture all forms of AKI. Consequently, a multimarker approach may provide superior diagnostic accuracy and prognostic information [18].

Future research should focus on validating biomarker panels across diverse clinical settings, establishing standardized thresholds, and integrating biomarker-guided decision-making into routine patient care. Such advancements could significantly improve early diagnosis, reduce AKI-related complications, and enhance long-term renal outcomes.

CONCLUSION

Emerging biomarkers have transformed the approach to AKI diagnosis by enabling detection of renal injury before conventional markers become abnormal. NGAL, KIM-1, IL-18, L-FABP, and TIMP-2 × IGFBP7 demonstrate superior sensitivity and specificity compared with serum creatinine. Among these, TIMP-2 × IGFBP7 and NGAL exhibit the highest diagnostic accuracy. Incorporation of these biomarkers into clinical practice may facilitate earlier intervention, improve patient outcomes, and reduce progression to chronic kidney disease. Further large-scale studies are necessary to standardize their use and establish cost-effective clinical protocols.

REFERENCES

1. Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury. *Lancet*. 2015;385(9987):2616-2643.
2. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol*. 2018;14(10):607-625.
3. Kidney Disease: Improving Global Outcomes (KDIGO). Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2(1):1-138.
4. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol*. 2009;20(3):672-679.
5. Macedo E, Malhotra R, Claire-Del Granado R, et al. Defining urine output criterion for AKI. *Nephrol Dial Transplant*. 2011;26(2):509-515.
6. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease. *N Engl J Med*. 2014;371(1):58-66.
7. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. *Annu Rev Pharmacol Toxicol*. 2008;48:463-493.
8. Mishra J, Dent C, Tarabishi R, et al. NGAL as a biomarker for acute renal injury. *Lancet*. 2005;365(9466):1231-1238.
9. Han WK, Bailly V, Abichandani R, et al. Kidney injury molecule-1 as a biomarker of proximal tubular injury. *Kidney Int*. 2002;62(1):237-244.

10. Parikh CR, Abraham E, Ancukiewicz M, et al. Urine IL-18 as an early diagnostic marker for AKI. *Kidney Int.* 2005;68(1):190-197.
11. Portilla D, Dent C, Sugaya T, et al. Liver-type fatty acid-binding protein as a biomarker of AKI. *Kidney Int.* 2008;73(4):465-472.
12. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell-cycle arrest biomarkers in AKI. *Crit Care.* 2013;17(1):R25.
13. Kellum JA, Lameire N. Diagnosis, evaluation and management of AKI. *Kidney Int Suppl.* 2013;3(1):19-36.
14. Haase M, Bellomo R, Devarajan P, et al. Accuracy of NGAL in diagnosing AKI: meta-analysis. *Am J Kidney Dis.* 2009;54(6):1012-1024.
15. Sabbiseti VS, Waikar SS, Antoine DJ, et al. Blood KIM-1 as a biomarker of AKI. *J Am Soc Nephrol.* 2014;25(10):2177-2186.
16. Bihorac A, Chawla LS, Shaw AD, et al. Validation of cell-cycle arrest biomarkers for AKI risk assessment. *Am J Respir Crit Care Med.* 2014;189(8):932-939.
17. Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on AKI biomarkers. *Intensive Care Med.* 2020;46(12):2415-2418.
18. Coca SG, Yalavarthi R, Concato J, et al. Biomarkers for the diagnosis and risk stratification of AKI. *Kidney Int.* 2008;73(9):1008-1016.