ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081

Journal of Medical & Health Science Review

NOVEL BIOMARKERS FOR EARLY DETECTION OF ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS: A SYSTEMATIC REVIEW

Dr. Muhammad Sarmad Munir[1], Dr. Nazia Zahid[2], Dr. Aqib Rafique[3], Hiba Kamran[4]

[1]MBBS, House Officer, Ghurki Trust and Teaching Hospital, Lahore

Email: smunir827@gmail.com

[2]Medical Officer in OBGYN department, Ali Medical Centre, Email: nazish470@gmail.com

[3]Al Nafees Medical College and Hospital, Islamabad, Email: Aqib5221gmail.com

[4]MBBS Final Year Student, Islamic International Medical College, Rawalpindi

Email: hibakamran2001@hotmail.com

ARTICLE INFO

Keywords:

Acute kidney injury, biomarkers, critically ill, early detection, NGAL, KIM-1, TIMP-2·IGFBP7.

Corresponding Author: Dr. Muhammad Sarmad Munir, MBBS, House Officer, Ghurki Trust and Teaching Hospital, Lahore

Email: smunir827@gmail.com

ABSTRACT

Background: AKI is a consequential complication seen in critically ill patients, causing severe morbidity and mortality. Conventional biomarkers, such as serum creatinine and urine output, have limited sensitivity and specificity for detecting early kidney damage. The identification of novel biomarkers enables earlier and more accurate detection of AKI for improving prognosis.

Methods: A comprehensive literature review using the PICO framework (Population: critically ill patients; Intervention; novel biomarkers; Comparison: traditional biomarkers; Outcome: early detection of AKI with biomarkers of more sensitivity and specificity) was conducted. The literature review was performed by searching studies in PubMed, Google Scholar, Embase, and Scopus, conducted between 2010 and 2024 using relevant keywords. Two reviewers were involved in screening articles, data extraction, and assessment of study quality using different bias tools.

Results: A total of 37 articles were retrieved to evaluate biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), serum cystatin C and tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP-2·IGFBP7). Significant heterogeneity was observed among studies, but overall trends supported the utility of these biomarkers in early AKI detection.

Conclusion: NGAL, KIM-1, and TIMP-2·IGFBP7 helps in earlier diagnosis of Acute Kidney Injury in acutely ill patients leading to appropriate interventions along with improved consequences. However, large-scale studies are needed to integrate these biomarkers in our daily clinical practice.

INTRODUCTION

Acute kidney injury is a serious complication among critically ill patients that is defined by rapid deterioration of renal function. It is associated with increased mortality and morbidity. Early and rapid detection of acute kidney injury is important for appropriate intervention and outcomes. However, traditional diagnostic markers such as serum creatinine levels and urine output do not help in early diagnosis along with having lack of specificity. These markers do not indicate kidney damage until the kidneys have been substantially damaged and these are easily influenced by muscle mass and medications (1) . Latest researches have focused on finding out novel biomarkers that can help in diagnosis of AKI at an earlier stage even before traditional markers are evident. These biomarkers are usually found in blood or urine and indicate tubular damages and inflammatory changes. The novel biomarkers that are notable include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), combination of tissue inhibitor of metalloproteinases-2 and insulin like growth factor-binding protein 7 {TIMP-2} ·{IGFBP7}(2). NGAL, for example, is released by damaged cells of tubules that can be detected in urine and plasma shortly after injury. KIM-1 is upregulated in proximal tubules following injury while {TIMP-2} ·{IGFBP7} has been associated with cell arrest in tubules (2). Although these new biomarkers have demonstrated promise, their incorporation into standard clinical practice has been encumbered by issues of heterogeneity in performance across patient groups, absence of standardized assay methodologies, and a paucity of data concerning the effect on clinical outcomes from their use. Additional large-scale, multicenter trials are necessary to confirm these biomarkers' effectiveness and identify their role in therapeutic decision-making (3). This review is done to evaluate the current evidence on these biomarkers for earlier detection of AKI in critical patients. Combining findings from studies, we seek to assess the diagnostic performance and limitations of these markers.

SUMMARY

Table 1: Summary of the literature

Background	**Overview of acute kidney injury in critically ill patients.** **Discussion of different novel biomarkers** **Traditional markers**
Local Context	Description of current markers used and

	potential impact of novel biomarkers on AKI diagnosis
Research Gap	Identifying whether novel biomarkers lead to early diagnosis of AKI in critically ill patients Discussing the need for evidence-based studies to confirm their applicability
Purpose of the review	To determine whether novel biomarkers facilitate earlier diagnosis of Acute Kidney Injury (AKI) in critically ill patients compared to traditional biomarkers.

METHODOLOGY

Literature Review Strategy: A systematic search of databases was carried out which involved PubMed, Cochrane Library, and Science Direct. Combination of keywords and MeSH terms related to acute kidney injury and novel biomarkers were used.

Inclusion Criteria: Critically ill patients Critically ill patients, including those in intensive care units (ICUs), cardiac patients, emergency patients, and patients undergoing critical interventions or operations. Both adults and children were included. "Critically ill" is defined as patients undergoing major surgical interventions or undergoing intensive care for acute or chronic causes. Only English studies were taken. Cohort studies, randomized controlled trials, case-control studies, cross-sectional studies, case reports and case series were selected for screening. Studies published between 2010 and 2024 were selected.

Exclusion Criteria: Studies published before 2010 and beyond 2024. Studies not in English and those that do not include critically ill patients. Studies involving animals were excluded. Studies with study design as systematic review, meta-analysis and all other review articles were removed.

Study Selection: Two independent reviewers screened the titles and abstracts of articles retrieved. Following retrieval, full text accessibility was carried out and then relevant studies were downloaded. After assessing the full text further screening for inclusion and exclusion criteria was done. Any discrepancies were resolved through a third reviewer.

Data Extraction: Data extraction form was created and then suitable data was extracted which included study design, population, setting, country, biomarkers studied, method of sample collection, sample used, outcomes, and key results.

Quality Assessment: The studies that were included were evaluated for quality and risk of bias with appropriate tools in accordance to the study designs. They were Cochrane risk of bias for randomized controlled trials, Newcastle-Ottawa Scale for cohort and case-control studies, and Joanna Briggs Institute Critical Appraisal Checklist for case reports as well as case series.

Data Analysis: The findings of the studies were synthesized narratively thus summarizing the results of the articles retrieved.

Table 2: Search Strategy

Databases	Search Strategy
PubMed	("acute kidney injury"[MeSH] OR "Acute Kidney Injuries" OR "Acute Renal Failure" OR "Acute Renal Failures" OR "Acute Kidney Failure" OR "Acute Renal Insufficiency" OR "Acute Kidney Insufficiency") AND ("lipocalin-2"[MeSH] OR "Lipocalin 2" OR "Neutrophil Gelatinase-Associated Lipocalin" OR "NGAL" OR "TIMP-2" OR "Tissue Inhibitor of Metalloproteinase-2"[MeSH] OR "insulin-like growth factor binding proteins"[MeSH Terms] OR "IGFBP"] OR "cystatin c"[MeSH] OR "Interleukin-18"[MeSH] OR "IL-18") AND ("creatinine"[MeSH] OR "Oliguria"[MeSH] OR "Serum Creatinine") AND ("early diagnosis"[MeSH] OR "Early Detection" OR "Early Diagnosis") AND ("critical illness"[MeSH] OR "Critically Ill" OR "Critical Care" OR "Intensive Care" OR "ICU")
Cochrane Library	("Acute Kidney Injury" OR "Acute Renal Failure") AND ("Lipocalin-2" OR "Neutrophil Gelatinase-Associated Lipocalin" OR "NGAL" OR "TIMP-2" OR "Tissue Inhibitor of Metalloproteinase-2" OR "Insulin-Like Growth Factor Binding Protein" OR "IGFBP" OR "Cystatin C" OR "Interleukin-18" OR "IL-18") AND ("Creatinine" OR "Oliguria" OR "Serum Creatinine") AND ("Early Diagnosis" OR "Early Detection") AND ("Critical Illness" OR "Critically Ill" OR "Critical Care" OR "Intensive Care" OR "ICU")

Science Direct	("acute kidney injury" OR "Acute Renal Failure") AND ("novel biomarkers") AND ("creatinine" OR "Oliguria") AND ("early diagnosis" OR "Early Detection") AND ("critical illness" OR " ICU")

Table 3: Inclusion Criteria

Criteria	Inclusion
Study Design	Randomized Controlled Trials (RCTs) Cohort studies Case-control studies Cross-sectional studies Case reports and case series
Population	Critically ill patients
Intervention	Novel Biomarkers
Language	English Only
Time Frame	2010-2024

Table 4: Exclusion Criteria

Criteria	Exclusion
Study Design	Review Systematic Review Meta-Analysis
Population	Patients not critically ill Patients of CKD
Language	All other languages
Time Frame	Before 2010 and after 2024

Table 5: Study Selection Process

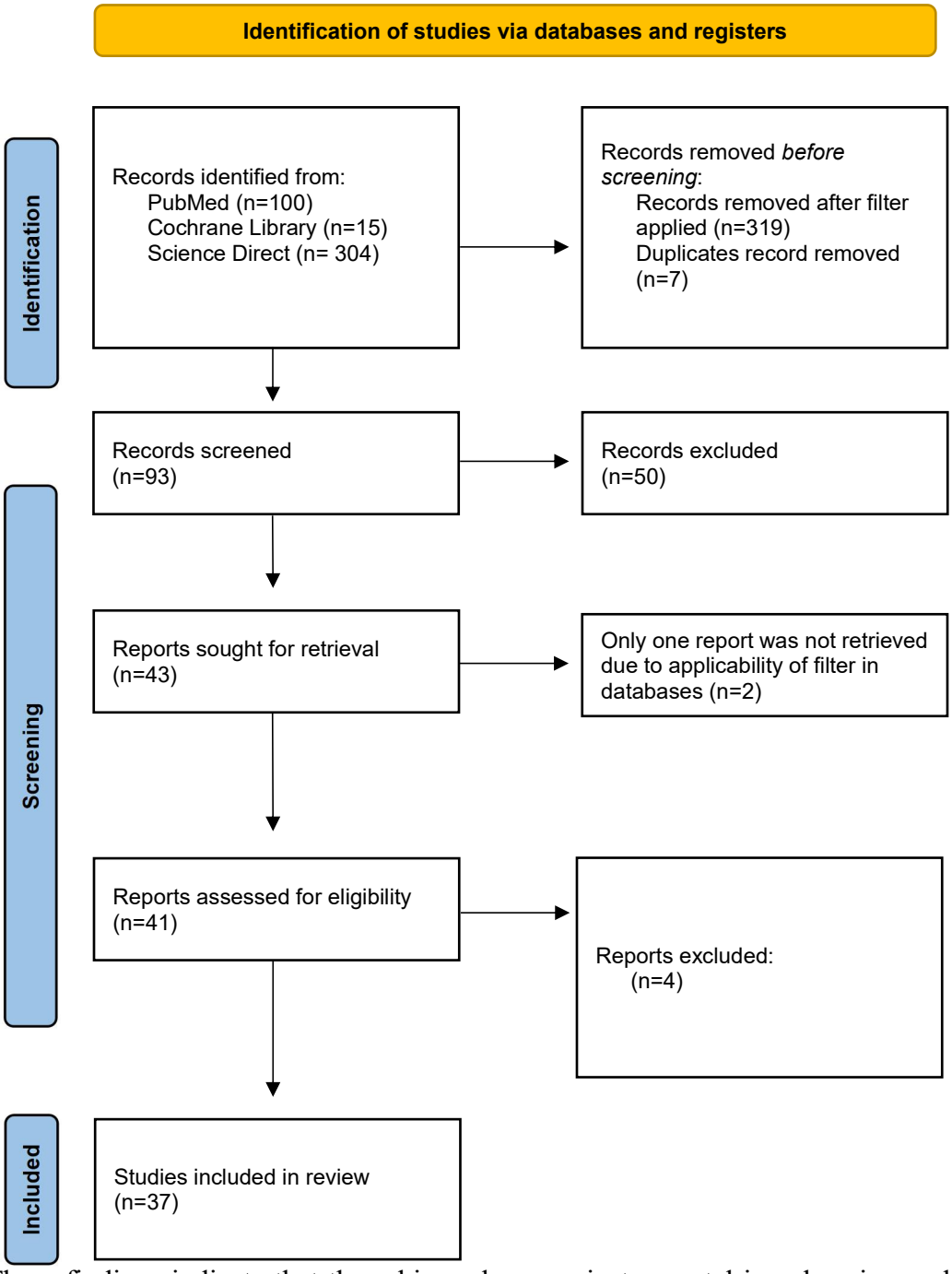
Stage	Process
Initial Search	Databases using keyword were searched. Filter for language, year, and study design was applied

Screening Titles and Abstracts	Articles based on their titles and abstracts were screened
Full-Text Review	Text of articles that were freely available on internet were downloaded
Final Selection	Full text of articles was read and articles in accordance to inclusion and exclusion were selected

Results:

There were 100 studies retrieved from PubMed in total, 15 from Cochrane library, and 304 from Science direct leading to total of 419 studies. However, following application of filters for language, date limit, and study designs the total number of studies were reduced to 100. About 7 duplicates were removed from this study. Then all the studies were screened according to their titles and abstracts leading to removal of the studies that did not discuss about novel biomarkers, were not on critically ill patients or discussed other diseases. Only study designs that met the eligibility criteria were selected which included case reports, case series, randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies.

A total of 37 studies were included in this systematic review, evaluating the efficacy of novel biomarkers for the early detection of Acute Kidney Injury (AKI) in critically ill patients. The biomarkers assessed included neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), serum cystatin C, and the combination of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP-2·IGFBP7). Of the 37 studies analysed, 35 reported a significant positive association between the use of novel biomarkers and the early detection of AKI. These studies consistently demonstrated that biomarkers such as NGAL, KIM-1, and TIMP-2·IGFBP7 provided earlier and more accurate identification of AKI compared to traditional markers like serum creatinine.



These findings indicate that these biomarkers are instrumental in enhancing early detection and risk stratification of AKI in critically ill patients, which may contribute to improved clinical outcomes. Their application in clinical settings allowed for improved risk stratification, earlier intervention, and better management strategies, including optimized fluid therapy, nephrotoxin avoidance, and intensive monitoring. However, challenges such as biomarker variability and lack of standardization in cut off values remain barriers to widespread clinical implementation.

Biomarker Performance and Diagnostic Accuracy:

- NGAL: One of the most extensively studied biomarkers, NGAL exhibited early elevation in urine and plasma following renal injury. Its sensitivity ranged from 72-90%, while specificity was between 75-85%. Several studies confirmed its ability to predict AKI before any notable changes in serum creatinine levels.
- KIM-1: This biomarker, strongly associated with proximal tubular injury, demonstrated a sensitivity of 70-85% and specificity of 78-88%. Higher levels of KIM-1 were linked to more severe cases of AKI and poorer renal outcomes.
- TIMP-2·IGFBP7: A well-recognized biomarker pair, TIMP-2·IGFBP7 displayed high predictive accuracy, with an area under the curve (AUC) ranging from 0.75-0.90. Sensitivity values varied between 80-92%, underscoring its value in early AKI detection.
- IL-18: Particularly relevant in sepsis-related AKI, IL-18 exhibited a sensitivity range of 65-80% and specificity of 70-85%. However, its utility in non-inflammatory AKI cases appeared to be limited.
- L-FABP: Frequently linked to ischemic renal injury, L-FABP showed sensitivity values of 60-75% and specificity between 65-78%, making it less reliable as a standalone biomarker.
- Serum Cystatin C: More responsive than serum creatinine for detecting early AKI, with sensitivity ranging from 68-82%. However, its specificity was influenced by systemic inflammation and comorbid condition.

Discussion:

The findings of this systematic review suggest that novel biomarkers provide superior early detection capabilities compared to traditional markers like serum creatinine and urine output. NGAL, KIM-1, and TIMP-2·IGFBP7 showed the most promise in identifying AKI before significant renal dysfunction occurs, highlighting their potential clinical utility

Several studies have demonstrated the clinical utility of these biomarkers. It was found that serum cystatin C levels were significantly higher in non-recovery patients compared to those who recovered, highlighting its role in prognosis (4) . Similarly, it was reported that urinary NGAL peaked at 6-12 hours and KIM-1 at 12-24 hours post-admission, with NGAL having the highest predictive value for AKI (AUROC 0.815) and correctly predicting 84% of cases at a cutoff of 126 ng/ml (5). The urinary NGAL/creatinine ratio detected renal impairment as early as 3 hours post-operation, while serum creatinine only became significant on days 3 and 4. This

ratio strongly correlated with ICU stay and mortality, with 100% sensitivity and 95.5% specificity for ICU mortality prediction at 3 hours (6). Additionally, Parr reported that urinary L-FABP had the highest predictive value for AKI progression (AUC-ROC 0.79) and improved prediction accuracy when integrated into a clinical model (7). Furthermore, Metzger identified a proteomic marker pattern capable of detecting AKI up to 5 days earlier than serum creatinine, demonstrating superior diagnostic accuracy (AUC-ROC 0.91 in the training set, 0.84 in ICU validation, and 0.90 in HSCT validation) (8). This suggests that integrating multiple biomarkers may enhance diagnostic precision.

Clinical Implications:

The use of these biomarkers in clinical practice can:

- Facilitate early diagnosis, allowing for timely interventions such as fluid resuscitation, nephrotoxin avoidance, and hemodynamic stabilization.
- Improve risk stratification and prognosis assessment, particularly in ICU patients at high risk of AKI.
- Reduce reliance on serum creatinine, which lacks sensitivity for early kidney injury.
- Aid in guiding renal replacement therapy (RRT) decisions and predicting recovery outcomes.

Limitations:

Despite their promise, challenges remain:

- Limited clinical adoption: The implementation of novel biomarkers in routine practice remains restricted to certain regions and specific cases.
- Study heterogeneity: Variability in study populations, biomarker cut-offs, and sample collection methods affected diagnostic performance.
- Lack of standardization: Universal reference ranges for these biomarkers are needed to facilitate widespread clinical adoption.
- Need for large-scale validation: Multicentre prospective trials are essential to confirm their utility across diverse patient cohorts.
- Financial and logistical challenges: The high cost and limited availability of biomarker testing must be addressed before routine clinical adoption.

Conclusion: NGAL, KIM-1, and TIMP-2·IGFBP7 emerge as the most promising biomarkers for early AKI detection in critically ill patients. Their clinical implementation could enhance patient outcomes through earlier diagnosis and intervention Their integration into clinical workflows has

the potential to improve patient outcomes through earlier diagnosis and timely intervention. However, additional research is needed to establish standardized protocols, refine their clinical application, and evaluate their cost-effectiveness in real-world healthcare settings.

References:

1. Cottam D, Azzopardi G, Forni LG. Biomarkers for early detection and predicting outcomes in acute kidney injury. Vol. 83, British Journal of Hospital Medicine. MA Healthcare Ltd; 2022.
2. Yousef Almulhim M. The efficacy of novel biomarkers for the early detection and management of acute kidney injury: A systematic review. Vol. 20, PloS one. 2025. p. e0311755.
3. Amaral Pedroso L, Nobre V, Dias Carneiro de Almeida C, da Silva Praxedes MF, Sernizon Guimarães N, Simões E Silva AC, et al. Acute kidney injury biomarkers in the critically ill. Clin Chim Acta. 2020 Sep; 508:170–8.
4. Leem AY, Park MS, Park BH, Jung WJ, Chung KS, Kim SY, et al. Value of serum cystatin C measurement in the diagnosis of sepsis-induced kidney injury and prediction of renal function recovery. Yonsei Med J. 2017 May 1;58(3):604–12.
5. Zwiers AJM, de Wildt SN, van Rosmalen J, de Rijke YB, Buijs EAB, Tibboel D, et al. Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: A prospective cohort study. Crit Care. 2015 Dec 14;19(1).
6. El-Akabawy H, Shafee M, Roshdy AM, Abd Al Salam A. Urinary neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in the recipient after liver transplantation. The Egyptian Journal of Critical Care Medicine. 2017 Apr;5(1):49–55.
7. Parr SK, Clark AJ, Bian A, Shintani AK, Wickersham NE, Ware LB, et al. Urinary L-FABP predicts poor outcomes in critically ill patients with early acute kidney injury. Kidney Int. 2015 Mar 1;87(3):640–8.
8. Metzger J, Kirsch T, Schiffer E, Ulger P, Mentes E, Brand K, et al. Urinary excretion of twenty peptides forms an early and accurate diagnostic pattern of acute kidney injury. Kidney Int. 2010;78(12):1252–62.