Navigating the landscape: a comprehensive review of biomarkers in acute kidney injury

Seema Umate | Minakshi Choudhary | Akhtaribano Sayyad | Ranjana Sharma | Pratibha Wankhede | Savita Pohekar | Karishma Dod | Bharti Tamgire | Roshan Umate | Mayur Wanjari

Department of Nursing, Shalinitai Meghe College of Nursing, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
Department of Medical Surgical Nursing, Shalinitai Meghe College of Nursing, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
Department of Community Health Nursing, Shalinitai Meghe College of Nursing, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
Department of Research and Development, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

Abstract This comprehensive review explored the evolving landscape of biomarkers of acute kidney injury (AKI), emphasizing their critical role in early detection, monitoring, and prognostication. The examination included functional biomarkers (serum cystatin C, NGAL, KIM-1), tubular injury biomarkers (NAG, L-FABP, and IL-18), inflammatory biomarkers (CRP, TNF-α, and IL-6), and oxidative stress biomarkers (MDA, SOD, and catalase). These biomarkers offer nuanced insights into specific facets of renal injury, aiding in differentiating prerenal and intrinsic renal injury and providing a more holistic understanding of AKI pathophysiology. The implications for clinical practice are profound, with biomarkers presenting valuable tools for personalized patient management, early intervention, and improved outcomes. Future research directions should focus on identifying emerging biomarkers, technological advancements, refining integration strategies, and addressing standardization and cost-effectiveness for seamless integration into routine clinical practice. This comprehensive approach positions AKI biomarkers as pivotal in advancing diagnostic precision and intervention strategies in the dynamic landscape of acute kidney injury.

Keywords: oxidative stress, inflammatory markers, early detection, renal dysfunction, biomarkers, acute kidney injury (AKI)

1. Introduction

Acute kidney injury (AKI) represents a critical medical condition characterized by a sudden and rapid decline in renal function. This multifaceted syndrome is often associated with various etiologies, ranging from ischemic injury to nephrotoxic exposures. Understanding the dynamics of AKI is crucial, as it poses a significant threat to patient outcomes and can lead to chronic kidney disease if not promptly identified and managed (Goyal et al., 2024).

The time sensitivity of AKI treatment underscores the importance of early detection and continuous monitoring. Rapid identification allows timely intervention, potentially mitigating the severity of renal damage and improving patient prognosis. The traditional diagnostic methods, such as serum creatinine and blood urea nitrogen, may not exhibit sensitivity early during AKI. Hence, a compelling need arises for more nuanced and responsive diagnostic tools (Chen et al., 2023).

Biomarkers have emerged as promising tools in the field of AKI, offering a means to detect renal injury at earlier stages than conventional methods. These molecular indicators can provide valuable insights into the pathophysiological processes occurring within the kidneys. Understanding the intricate roles of these biomarkers in the context of AKI not only facilitates early diagnosis but also contributes to a deeper comprehension of the underlying mechanisms driving renal dysfunction (Vaidya et al., 2008).

This review aimed to comprehensively explore and evaluate the landscape of biomarkers of acute kidney injury. By examining the current state of knowledge surrounding various biomarkers, their classifications, and their respective contributions to early detection and prognosis, this review aims to provide a holistic understanding of the roles of these markers in the clinical context. Furthermore, we seek to highlight the challenges and limitations associated with their application and propose potential directions for future research in this critical area of nephrology. Through this exploration, we aim to contribute to ongoing efforts to refine diagnostic approaches and enhance patient outcomes in acute kidney injury patients.
2. Review

2.1. Current diagnostic methods for AKI

2.1.1. Serum creatinine and blood urea nitrogen (BUN) levels

Serum creatinine and blood urea nitrogen (BUN) have historically been found to be fundamental components of the acute kidney injury (AKI) diagnostic toolbox. These traditional markers are preferred for their widespread accessibility, cost-effectiveness, and routine integration into clinical practice. Serum creatinine, which is derived from muscle metabolism, and BUN, a byproduct of protein catabolism, are routinely measured to evaluate renal function (Manoeuvrier et al., 2017). The concentrations of these markers serve as essential indicators of kidney efficiency in filtering and excreting waste products. Deviations from normal levels indicate potential impairment in kidney function and prompt further investigation. The routine monitoring of serum creatinine and BUN levels provides clinicians with valuable insights into the overall renal health of patients, revealing the initial steps in the diagnostic pathway for AKI. Despite their ubiquity, it is essential to acknowledge the limitations of these traditional markers, particularly in their sensitivity to early-stage renal dysfunction. This factor has fuelled the exploration and development of more sensitive and specific biomarkers for improved diagnostic precision in acute kidney injury (Edelstein, 2008).

2.1.2. Limitations of Traditional Markers

Despite the extensive use of serum creatinine and blood urea nitrogen (BUN) levels for diagnosing acute kidney injury (AKI), these traditional markers are associated with notable limitations, particularly in the early stages of renal dysfunction. The lack of sensitivity and specificity of these methods poses challenges in capturing subtle changes in kidney function during the initial phases of injury. This limitation is critical because it may delay the identification of AKI, potentially impacting the timely initiation of therapeutic interventions. Additionally, the interpretability of these markers could be improved by various factors, including age, muscle mass, and hydration status (Simsek et al., 2013). The influence of these variables complicates the assessment of renal function and may lead to misinterpretations of marker levels. Furthermore, the delayed response of the serum creatinine concentration to changes in the glomerular filtration rate (GFR) adds a layer of complexity, limiting the effectiveness of these markers in the early detection of AKI. Recognizing and addressing these limitations is essential for advancing the field of AKI diagnostics and underscores the need for more sensitive and specific biomarkers to complement or replace traditional markers in certain clinical scenarios (Edelstein, 2008).

2.1.3. Need for More Sensitive and Specific Biomarkers

Acknowledging the limitations inherent in traditional markers, there is a rising awareness of the necessity for more sensitive and specific biomarkers in acute kidney injury (AKI) diagnosis. Pursuing these biomarkers is fuelled by the crucial need to identify renal injury at its earliest stages, paving the way for timely therapeutic interventions. The quest for such biomarkers is motivated by the understanding that traditional markers often fail to capture subtle changes in renal function during the initial phases of injury, potentially delaying the initiation of crucial interventions (Sriswat & Kellum, 2020). Sensitive biomarkers capable of detecting even minor alterations in renal function offer a critical window of opportunity for intervention before irreversible damage ensues. This recognition underscores a paradigm shift in the approach to AKI diagnosis, emphasizing the importance of precision and early detection in improving patient outcomes. The ongoing research and development of more advanced biomarkers exemplify a commitment to enhancing the diagnostic landscape and addressing the evolving needs of AKI management (Shah & Mehta, 2006).

2.2. Importance of biomarkers in AKI

2.2.1. Early detection and intervention

Biomarkers of acute kidney injury (AKI) play pivotal and primary roles in enabling early detection and intervention, addressing a critical need in renal health. Traditional markers, such as serum creatinine, often exhibit significant changes only after substantial renal damage, limiting their effectiveness in the early stages of AKI. In contrast, biomarkers, particularly those reflective of early cellular stress or injury, offer a more sensitive and timelier window into evolving renal dysfunction. The ability of these devices to detect subtle changes before overt clinical symptoms emerge is instrumental in facilitating early identification of AKI (Teo & Endre, 2017). This early detection, in turn, enables clinicians to promptly initiate therapeutic strategies to mitigate further renal damage. The significance of early intervention lies in its potential to prevent the progression of AKI, optimize patient outcomes, and contribute to the overall improvement of renal health. The incorporation of biomarkers for early detection and intervention marks a transformative shift in the approach to AKI management, emphasizing a proactive stance toward preserving renal function and enhancing patient care (Xiao et al., 2022).
2.2.2. Predictive Value for Renal Outcomes

The role of biomarkers in acute kidney injury (AKI) extends beyond early detection to encompass a crucial prognostic dimension, providing valuable insights into the anticipated trajectory of renal function and the overall prognosis for the patient. Through continuous monitoring of specific biomarkers, clinicians can assess the severity of renal insult and predict the likelihood of various renal outcomes, including recovery or progression to chronic kidney disease (CKD). This predictive capability is a powerful tool in personalized patient management, allowing for more targeted and informed interventions based on the individualized risk profile inferred from biomarker patterns (Srisawat & Kellum, 2020). The ability to anticipate renal outcomes enhances the precision of clinical decision-making, guiding healthcare professionals in optimizing therapeutic strategies and improving long-term renal health outcomes for patients affected by AKI. Integrating biomarkers for predictive purposes represents a significant advancement in renal care, facilitating a more nuanced and individualized approach to patient management in the complex landscape of acute kidney injury (Yuan et al., 2020).

2.2.3. Differentiating Prerenal and Intrinsic Renal Injury

An essential facet of biomarkers in acute kidney injury (AKI) lies in their ability to distinguish between prerenal and intrinsic renal injury. Prerenal causes, typically associated with reduced blood flow to the kidneys, may be reversible with appropriate interventions, highlighting the importance of prompt and targeted therapeutic measures. In contrast, intrinsic renal injury often indicates structural damage to kidney tissue, necessitating a distinct approach to management. Biomarkers that reflect specific aspects of renal function or injury mechanisms play pivotal roles in distinguishing between these two types of injury (Makris & Spanou, 2016a). By assessing the unique signatures captured by these biomarkers, clinicians can make informed decisions about the nature and origin of renal injury, guiding the selection of appropriate therapeutic strategies. This differentiation is crucial in optimizing patient care, as it enables healthcare professionals to tailor interventions based on the underlying pathophysiology of AKI, ultimately contributing to more effective and personalized management strategies for individuals affected by renal injury (Brazzelli et al., 2022).

2.3. Functional biomarkers

2.3.1. Serum Cystatin C

Serum cystatin C is a critical functional biomarker in acute kidney injury (AKI). This low-molecular-weight protein is produced by all nucleated cells at a constant rate and is freely filtered by the glomerulus. Unlike traditional markers such as creatinine, cystatin C is less influenced by factors such as age, muscle mass, and diet, making it a more reliable indicator of the glomerular filtration rate (GFR). Elevated levels of serum cystatin C indicate a decreased glomerular filtration rate (GFR) and have been recognized as an early and sensitive marker for detecting renal dysfunction in the early stages of AKI (Murty et al., 2013).

2.3.2. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is another prominent functional biomarker implicated in the early detection of acute kidney injury. NGAL is expressed by renal tubular cells and neutrophils in response to injury or inflammation. Elevated levels of NGAL in urine or serum can occur within hours of renal insult, providing a rapid and sensitive indication of tubular damage. Even before traditional markers are used, the ability of NGAL to detect injury at early positions is a valuable tool for early diagnosis and risk stratification in AKI patients (Haase-Fielitz et al., 2014).

2.3.3. Kidney injury molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein expressed on the apical membrane of proximal tubular cells. In response to injury, KIM-1 is upregulated and shed into the urine, making it a specific marker of tubular damage. KIM-1 has demonstrated utility in distinguishing between prerenal and intrinsic renal injury and has shown promise in predicting the progression of AKI to chronic kidney disease. KIM-1 is a functional biomarker that contributes to the growing arsenal of tools for the early detection and characterization of renal injury (Han et al., 2002).

2.4. Tubular injury biomarkers

2.4.1. N-acetyl-beta-D-glucosaminidase (NAG)

N-acetyl-beta-D-glucosaminidase (NAG) is a prominent tubular injury biomarker associated with acute kidney injury (AKI). This lysosomal enzyme is present in the proximal tubular cells of the kidney. In response to tubular damage, NAG is released into the urine, making it a reliable indicator of early renal injury. Elevated levels of NAG in urine suggest proximal tubular cell damage and are correlated with the severity of AKI. Monitoring NAG levels contributes to the early...
identification and characterization of tubular injury, allowing timely intervention to mitigate further renal damage (Yoo et al., 2021).

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

Liver-type fatty acid-binding protein (L-FABP) is another tubular injury biomarker with significant implications for acute kidney injury. L-FABP is expressed in proximal tubular cells and is crucial for intracellular fatty acid transport. Following tubular injury, L-FABP is released into the urine, making it a sensitive marker for the early detection of renal damage. The measurement of L-FABP levels has shown promise in predicting the severity of AKI and differentiating between prerenal and intrinsic renal injury. Its rapid response to tubular injury positions it as a valuable tool in the diagnostic armamentarium for AKI (Matsui et al., 2011).

2.4.3. Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is a cytokine that is a tubular injury biomarker in acute kidney injury. Under normal conditions, IL-18 is present at low concentrations in renal tubular cells. However, in response to ischemia, inflammation, or other forms of tubular injury, IL-18 is released into the urine. Elevated urinary IL-18 levels are associated with the severity of AKI and may indicate ongoing renal inflammation. Monitoring IL-18 levels contributes to a deeper understanding of the inflammatory component of tubular injury, aiding in risk stratification and guiding therapeutic interventions (Hirooka & Nozaki, 2021).

2.5. Inflammatory biomarkers

2.5.1. C-reactive protein (CRP)

C-reactive protein (CRP) is a well-established inflammatory biomarker with applications extending beyond cardiovascular diseases to acute kidney injury (AKI). CRP is produced in the liver in response to inflammation, infection, or tissue injury, and CRP levels increase rapidly. In the context of AKI, elevated CRP levels indicate the presence of systemic inflammation and can be indicative of renal injury. While CRP is a nonspecific marker, its measurement contributes to the overall assessment of the inflammatory response in AKI patients and aids in risk stratification (Li et al., 2023).

2.5.2. Tumor necrosis factor-alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that plays a pivotal role in the inflammatory response. In acute kidney injury, TNF-α is released as part of the immune response to injury or infection. Elevated levels of TNF-α have been associated with the development and progression of AKI. Monitoring TNF-α provides valuable information about the inflammatory milieu within the kidneys, aiding in the characterization of the underlying pathophysiology and influencing therapeutic decisions (Jang et al., 2021).

2.5.3. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a multifunctional cytokine that regulates immune response and inflammation. Elevated IL-6 levels have been observed in various inflammatory conditions, including acute kidney injury. As an inflammatory biomarker, IL-6 contributes to understanding the immune-mediated processes underlying AKI. Monitoring IL-6 levels may assist in assessing the severity of inflammation and guiding therapeutic strategies to modulate the immune response (Tanaka et al., 2014).

2.6. Oxidative stress biomarkers

2.6.1. Malondialdehyde (MDA)

Malondialdehyde (MDA) is a critical oxidative stress biomarker that reflects lipid peroxidation, a process associated with cellular damage caused by reactive oxygen species (ROS). In acute kidney injury (AKI), increased oxidative stress can lead to lipid peroxidation, leading to the formation of MDA. Elevated levels of MDA in tissues or biological fluids, such as urine, serve as indicators of oxidative damage and can indicate the severity of AKI. Monitoring MDA levels contributes to understanding the role of oxidative stress in renal injury and guides interventions aimed at mitigating oxidative damage (Gaweł et al., 2004).

2.6.2. Superoxide dismutase (SOD)

SOD is an antioxidant enzyme that plays a crucial role in the defense against oxidative stress. In acute kidney injury, the production of reactive oxygen species can overwhelm antioxidant defenses, leading to tissue damage. Measurement of SOD levels provides insights into the capacity of the antioxidant system to neutralize superoxide radicals. Reduced SOD
activity may indicate an impaired antioxidant defense mechanism, contributing to the oxidative stress associated with AKI (Nandi et al., 2019).

2.6.3. Catalase

Catalase is another antioxidant enzyme that plays a vital role in protecting cells from oxidative damage by converting hydrogen peroxide into water and oxygen. In the context of acute kidney injury, catalase activity may be altered due to increased oxidative stress. Monitoring catalase levels or activity can provide valuable information about the cellular response to oxidative stress and the potential impact on renal function. Understanding the status of catalase contributes to the broader picture of oxidative stress dynamics in AKI (Makris & Spanou, 2016b).

2.7. Challenges and limitations

2.7.1. Standardization Issues

The utilization of biomarkers in acute kidney injury (AKI) faces challenges related to standardization. Variability in laboratory methods, calibration, and assay techniques across different institutions and laboratories can impact the consistency and comparability of results. Standardizing protocols for sample collection, storage, and analysis are essential to ensure the reliability and reproducibility of biomarker measurements. Addressing these standardization issues is crucial for widely adopting biomarkers in clinical practice and research (Teo & Endre, 2017).

2.7.2. Interpretation challenges

Interpreting biomarker results in the context of AKI presents another set of challenges. Various factors, including age, sex, comorbidities, and medications, can influence biomarker concentrations. Additionally, the kinetics of biomarker release and clearance may differ among individuals, making it challenging to establish universal cutoff values for diagnosis or prognosis. Clinicians must consider the clinical context, patient characteristics, and specific biomarker dynamics to interpret results and make accurate informed clinical decisions (Hasson et al., 2022).

2.7.3. Cost considerations

Implementing biomarkers in AKI diagnostics introduces cost considerations that may pose challenges to widespread adoption. Developing and validating assays, ensuring standardization and routinely measuring biomarkers can incur additional expenses. Access to advanced biomarker testing may be limited in specific healthcare settings, hindering its widespread use. Balancing the potential clinical benefits with the associated costs is crucial to ensure the practicality and feasibility of integrating biomarkers into routine clinical practice (Devarajan, 2011).

2.8. Future directions

2.8.1. Emerging Biomarkers

The future of biomarkers for acute kidney injury (AKI) is promising because of the need to identify and validate emerging biomarkers. Ongoing research is likely to unveil novel markers that offer even greater sensitivity and specificity for the early detection and characterization of renal injury. Exploring the molecular and genetic signatures associated with AKI may lead to the discovery of innovative biomarkers that provide deeper insights into the pathophysiology of renal damage. As researchers continue to unravel the complexities of AKI, identifying and validating new biomarkers will be pivotal in enhancing diagnostic precision (Devarajan, 2008).

2.8.2. Advances in Technology

Advancements in technology are poised to revolutionize the landscape of AKI biomarkers. The integration of cutting-edge techniques, such as mass spectrometry, microfluidics, and point-of-care testing, can improve biomarker assay accuracy, speed, and cost-effectiveness. Miniaturized and portable devices may facilitate real-time monitoring of biomarkers at the bedside, enabling prompt clinical decision-making. As technology continues to evolve, it is anticipated that the diagnostic capabilities of AKI biomarkers will be further refined, allowing for more seamless integration into routine clinical practice (Basu et al., 2014).

2.8.3. Integration of Multiple Biomarkers for Increased Accuracy

The future of AKI biomarkers lies in integrating multiple markers to create a comprehensive diagnostic profile. The combination of functional, tubular injury, inflammatory, and oxidative stress biomarkers may lead to a more holistic understanding of the diverse mechanisms underlying renal injury. Multiple biomarker panels have the potential to improve diagnostic accuracy, enhance risk stratification, and provide valuable prognostic information. Integrated approaches may
also contribute to better differentiation between prerenal and intrinsic renal injury, guiding tailored therapeutic interventions. As research progresses, refining the integration of multiple biomarkers will likely be a pivotal focus for optimizing the clinical utility of these markers in AKI (Rosa et al., 2021).

3. Final Considerations

In conclusion, exploring biomarkers of acute kidney injury (AKI) has uncovered a dynamic landscape with far-reaching implications for clinical practice. The identified functional biomarkers, including serum cystatin C, NGAL, and KIM-1, offer sensitive tools for early detection, allowing timely interventions to mitigate renal damage. Tubular injury biomarkers such as NAG, L-FABP, and IL-18 provide insights into specific damage mechanisms, aiding in the differentiation between prerenal and intrinsic renal injury. Inflammatory biomarkers (CRP, TNF-α, and IL-6) and oxidative stress biomarkers (MDA, SOD, and catalase) contribute to a holistic understanding of AKI pathophysiology. Integrating these markers presents an exciting avenue for enhancing diagnostic accuracy and prognostication. Moving forward, the implications for clinical practice are significant, with biomarkers guiding personalized patient management strategies and improving outcomes. To harness the full potential of AKI biomarkers, future research should focus on exploring emerging markers, leveraging technological advancements, and refining integration approaches while addressing practical considerations such as standardization and cost-effectiveness. This holistic approach holds the key to advancing the role of biomarkers in acute kidney injury, shaping a more precise and effective paradigm for diagnosis and intervention in clinical settings.

Ethical considerations

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This research did not receive any financial support.

References


