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Review of the limitations of current biomarkers in acute kidney injury clinical practices

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Abstract

Acute kidney injury is a prevalent disease in hospitalized patients and is continuously increasing worldwide. Various efforts have been made to define and classify acute kidney injury to understand the progression of this disease. Furthermore, deviations from structure and kidney function and the current diagnostic guidelines are not adequately placed due to baseline serum creatinine values, which are rarely known and estimated based on glomerular function rate, resulting in misclassification of acute kidney injury staging. Hence, the current guidelines are still developing to improve and understand the clinical implications of risk factors and earlier predictive biomarkers of acute kidney injury. Yet, studies have indicated disadvantages and limitations with the current acute kidney injury biomarkers, including lack of sensitivity and specificity. Therefore, the present narrative review brings together the most current evidenced-based practice and literature associated with the limitations of the gold standard for acute kidney injury diagnoses, the need for novel acute kidney injury biomarkers, and the process for biomarkers to be qualified for diagnostic use under the following sections and themes. The introduction section situates the anatomy and normal and abnormal kidney functions related to acute kidney injury disorders. Guidelines in providing acute kidney injury definitions and classification are then considered, followed by a discussion of the disadvantages of standard markers used to diagnose acute kidney injury. Characteristics of an ideal acute kidney injury biomarker are discussed concerning sensitivity, specificity, and anatomic location of injury. A particular focus on the role and function of emerging biomarkers is discussed in relation to their applications and significance to the prognosis and severity of acute kidney injury. Findings show emerging markers are early indicators of acute kidney injury prediction in different clinical settings. Finally, the process required for a biomarker to be applied for diagnostic use is explained.

Keywords

Kidney, biomarker, limitations, acute, renal, ideal, biomarker discovery and development

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Introduction

Acute kidney injury (AKI) is a clinical syndrome that is a common problem in hospitalized patients and is classified by a rapid decline in kidney excretory function and accumulation of waste and nitrogen metabolism products.[1] The clinical practice guidelines of AKI is based upon the information provided by the Kidney Disease Improving Global Outcomes (KDIGO),[2,3] the most accepted and consent approach to the diagnostic criteria of AKI with serum creatinine (SCr) and estimated glomerular filtration rate (eGFR), alongside urine output leading to current classification and severity of the disease.[4] Although KDIGO clinical recommendations for AKI stress the significance of earlier detection of AKI to improve patient outcomes, AKI continues to be a clinical and therapeutic challenge for physicians due to limitations within the current implemented diagnostic biomarkers.[5]

Traditionally, the diagnosis of AKI is measured by the level of indirect biomarkers, that is, blood urea and nitrogen and SCr, but these methods lack sensitivity and specificity.

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Nevertheless, there are disagreements and controversies among clinicians for the clinical assessment and the role and effectiveness of biomarkers, such as SCr and eGFR.[6–9] In this context, assessment of structural kidney injury has notably been absent due to the current focus on glomerular filtration rate and functional kidney injury markers.[10] Nonetheless, many improvements are needed to discover novel biomarkers for kidney injury and increase the sensitivity and specificity of biomarkers of AKI. Thus, there is an urgency to discover early diagnostic markers that are reliable biomarkers of kidney injury in clinical practice, whereas these biomarkers can be used to predict structural injury to the kidney.

This narrative review aims to provide a better and comprehensive understanding of normal kidney function and AKI. Firstly, this article begins by describing current AKI definitions and classification guidelines and discussing the disadvantages of standard markers used in diagnosing AKI. Secondly, the characteristics of an ideal AKI biomarker are discussed in relation to its sensitivity, specificity, and anatomic location of the injury. Thirdly, the role and function of early and reliable biomarkers of AKI, with application and characterization as critical features of describing the etiology and anatomic location of the injury are dealt with. Finally, the process required for validating a biomarker for clinical diagnostic purposes is explained. Overall, this narrative review highlights the importance of developing novel biomarkers that are highly specific and sensitive in predicting and providing information to guide early therapeutic intervention for AKI.

Search strategy

The overall theme of this review article was the current therapeutic implications of AKI in practice. The following key points have been considered: kidney function, current AKI guidelines limitations, emerging biomarkers, and biomarker discovery and development.

The search was conducted via a broad range of healthcare-related databases. Multi-field database searches were conducted using Medline, PubMed, and Google Scholar from September 15, 2021, to November 20, 2023.

The researchers identified 63 papers using the following criteria: papers reporting on AKI classifications and definitions and papers focusing on current limitations in AKI diagnosis and therapeutic interventions. The topics included in these manuscripts are based on ideal characteristics of a kidney biomarker, emerging AKI biomarkers, and discovery and development of markers of AKI. Furthermore, editorials, letters, and case reports were excluded from this article. In addition, the search was focused on those articles published in English. The search terms included an abbreviated form of biomarker combined with the following terms: renal, kidney, acute, function, and validation.

Normal kidney function

The kidneys play a vital role in several physiological processes such as acid-base balance, fluid and electrolytes regulation, excretion of uremic toxin, and production of various hormones, that is, activation of cholecalciferol, erythropoietin, and renin. Moreover, Dhondup and Qian et al.[11] describe the mechanisms and pathways of glomerular filtration and tubular reabsorption and secretion, which play a vital role in maintaining the volume and composition of extracellular fluid in the body.[11] Normally, the glomerular filtration rate (GFR) is approximately 125 mL/min or 180 L/day 1–2 L of urine is excreted, and the rest of the 99% of filtrates are reabsorbed into the peritubular capillaries and return to the blood.[12] GFR primarily depends on three major factors, that is, blood pressure, filtration pressure, and permeability of the glomerular capillary walls. Hence, the GFR describes renal function, whereas creatinine clearance is the standard method to measure glomerular filtration. Furthermore, the amount of dissolved substance removed by the kidney is determined by comparing the creatinine levels in serum and urine.[13]

Nonetheless, the kidney filters unwanted substances from the blood and excretes them in the form of urine through the following processes: glomerular filtration, reabsorption, and secretion, certain molecules move across membranes by specific mechanisms, including active transport, diffusion, facilitated diffusion, and osmosis. The proximal tubule is the leading site of reabsorption while the other substances move through the loop of Henle, the distal tubule, and the collecting ducts. Using active transport and passive diffusion, a substance passes through the peritubular blood into the tubular lumen by tubular secretion (Figure 1). The homeostatic balance is maintained by hormones, such as antidiuretic (vasopressin) and aldosterone, which is synthesized by the renin–angiotensin system, playing a significant role in the regulation of tubular reabsorption and secretion of solutes and water.[14] Thus, an accumulation of metabolic products or electrolytes in the blood makes it difficult for the kidneys to regulate fluid balance and electrolyte instabilities, leading to AKI.

Acute kidney injury

AKI is characterized by an unexpected loss of kidney function that is defined based on SCr, a kidney excretory function marker, and urinary output, a quantitative marker of urine production.[16] Hence, AKI is one of the clinical cases that does not cover a single disease entity but covers a broad spectrum of disorders with different etiologies classified according to the cause and stage of the disease.[17] In this context, several diseases come under the AKI class: acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitis, pre-renal azotemia, and acute postrenal obstructive nephropathy. Once there is impaired

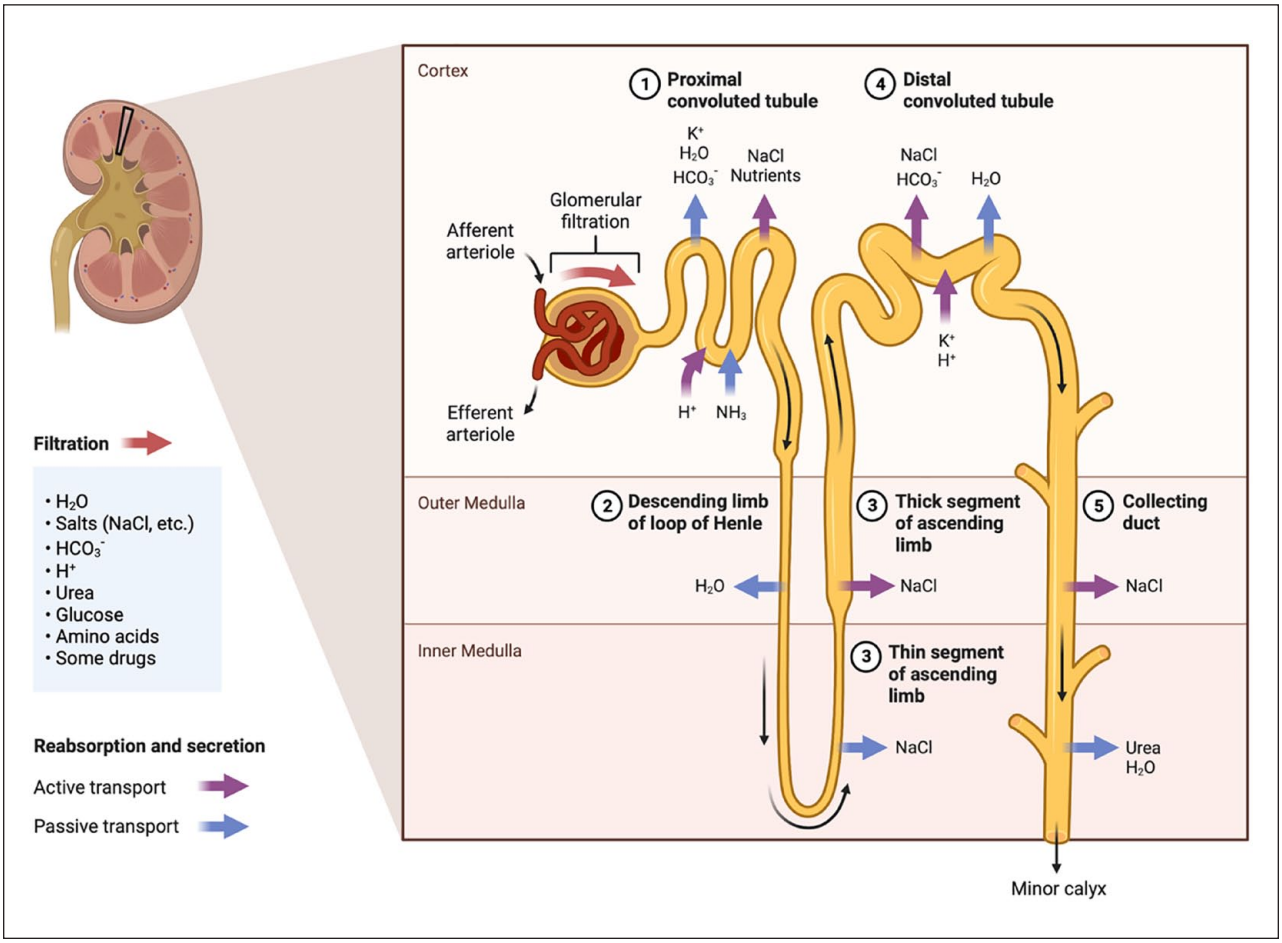

Figure 1. Kidney reabsorption and secretion.
Reprinted from "Kidney Reabsorption and Secretion" by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.[15]

renal blood flow, renal tubular cells are the target of hypoxic injury and disrupt intracellular calcium homeostasis, leukocytosis, cytokines release, and apoptosis.[18] And hence, it gives three primary causes of AKI, that is, pre/post-renal or intrinsic renal.

Etiology of AKI

Prerenal kidney failure in the case of AKI occurs due to poor perfusion of nephrons, which results in a decline in the GFR and blood flow to the kidney. In this case, tubular and glomerular functions can arise with the following combinations: hypoperfusion, hypovolemia, or hypotension renal vasoconstriction/vasodilation, which can lead to the development of renal arterial stenosis or aortic dismemberment.[19] In contrast, intrinsic renal causes are related to modifications or changes that impact the glomerulus or tubular segment of the kidney. For instance, acute tubular necrosis, acute interstitial nephritis, glomerulonephritis, and intratubular obstruction are just a few of the disorders that are associated with intrinsic renal AKI due to the presence of renal ischemia, sepsis, or nephrotoxins.[19,20] Lastly, postrenal causes are associated with obstructive circumstances due to blood clots, tumors, or renal calculi.[16]

AKI definitions and classifications

To have a consensus definition of AKI that distinguish it from other acute kidney disease (AKD) in clinical practice and research studies, KDIGO created a set of guidelines that are derived from the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) and AKI Network criteria.[21] RIFLE was first reported in 2004 by the Acute Dialysis Quality Initiative (ADQI) to diagnose and classify acute renal function impairments. RIFLE includes five stages: Risk, Injury, Failures, Loss of Kidney Function, and End-Stage kidney disease to define and classify the severity of AKI that details small changes in kidney function or urine output to kidney failure and, finally, end-stage renal disease. In 2007, the criteria were condensed into a 3-stage system by the AKD Network. The latest definition and classification guidelines of AKI were developed in 2012 by KDIGO, which is based

Table 1. Acute kidney injury classifications by KDIGO, RIFLE, and AKIN systems.

KDIGO	Urine output	RIFLE		AKIN
Serum creatinine		Class	Serum creatinine of GFR	
Stage One: 1.5–1.9 × baseline OR ⩾0.3 mg/dL increase	<0.5 mL/kg/h for 6-12h	Risk	Increase in SCr ⩾ 1.5 × baseline OR Decrease in GFR ⩾ 25%	Increase in SCr of ⩾ 0.3 mg/dL or 150%–200% baseline OR Urine output of <0.5 mL/kg/h for 6–12 h
Stage Two: 2–2.9 × baseline	<0.5 mL/kg/h for ⩾12 h	Injury	Increase in SCr ⩾ 2.0 × baseline OR Decrease in GFR ⩾ 50%	Increase in SCr to 200%–300% baseline OR Urine output of <0.5 mL/kg/h for 12 to 24 h
Stage Three: 3 × baseline OR Increase in SCr to ⩾ 4 mg/dL OR Initiation of renal replacement therapy	<0.3 mL/kg/h for ⩾24 h OR Anuria for ⩾ 12 h	Failure	Increase in SCr ⩾ 3.0 × baseline OR SCr ⩾ 4.0 mg/dL (354 μmol/L) OR Decrease in GFR ⩾ 75%	Increase in SCr to >300% baseline OR Increase in SCr by >0.5 mg/dL to ⩾ 4.0 mg/dL OR Urine output of <0.3 mL/kg/h for >24 h or anuria for >12 h OR Initiation of kidney replacement therapy
		Loss	Complete loss of kidney function >4 wk	
		End-stage kidney disease	ESRD > 3 mo	

AKIN: Acute Kidney Injury Network; ESRD: End-Stage Renal Disease; GFR: glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; RIFLE: Risk, Injury, Failure, Loss, and End Stage Renal Disease; SCr: serum creatinine.
KDIGO, AKIN including urine output, and RIFLE and AKIN.
Adapted from Reference Birkelo et al.[3] Copyright 2022 by the American Society of Nephrology.

on SCr and urine output.[3,22] Detailed information about the RIFLE, Acute Kidney Injury Network (AKIN), and KDIGO classification is described in Table 1.

Limitations of biomarkers in current AKI clinical practice

AKI is normally asymptomatic and usually diagnosed based on SCr, eGFR, and urine output. However, these markers are not specific and sensitive to glomerular filtration rate due to extra-renal factors, such as nutrition status, age, muscle mass, fluid resuscitation, and corticosteroid therapy.[18] In addition, SCr, which is nonspecific to structural injury, does not provide additional information on AKI etiology, prognosis, and treatment response.[23] Another issue is that SCr and GFR have a nonlinear relationship, indicating that vast changes in GFR only signify a slight change in SCr, which is usually neglected because the changes are within the reference range.[20] Additionally, modifications in SCr concentrations may not adequately show a true decline in GFR if the patient suffers from liver disease, sepsis, or muscle wasting.[24]

For these reasons, creatinine is not an ideal marker of AKI because the changes in creatinine level lag behind the decreases in the glomerular filtration rate and can take up to 24–36 h to show a significant increase after obvious renal insult (Figure 2). The most common method to measure serum creatinine in laboratory practice is focused on the Jaffe-based assays, which can cause interference with analytical techniques due to the presence of bilirubin and certain drugs such as trimethoprim and cimetidine, which are major limitations in laboratory-based assays. Hence, there are no standard methods to identify renal baseline function, which can result in misinterpretation of the results. Also, SCr levels are influenced by drugs competing with tubular secretions.[24] For instance, aspirin and methotrexate are known to compete for renal tubular secretion, which may cause SCr levels to oscillate without a modification in renal function.[24,25] Thus, SCr does not indicate the progression or recovery phase of AKI.[24]

In contrast, urine output is not considered a specific measurement of renal injury but shows kidney, metabolic, endocrine, or immunologic functions. According to the KDIGO criteria for AKI, urine output must show that oliguria has been present for at least 6 h.

The lack of early markers of renal failure contributes significantly to the high mortality and morbidity rate associated with AKI. Due to the delay of AKI identification, there are many missed opportunities for therapeutic intervention during the time window where AKI can be reversed.[26]

Early diagnosis of AKI is vital because it allows time for critical therapeutic implications for AKI treatment and can

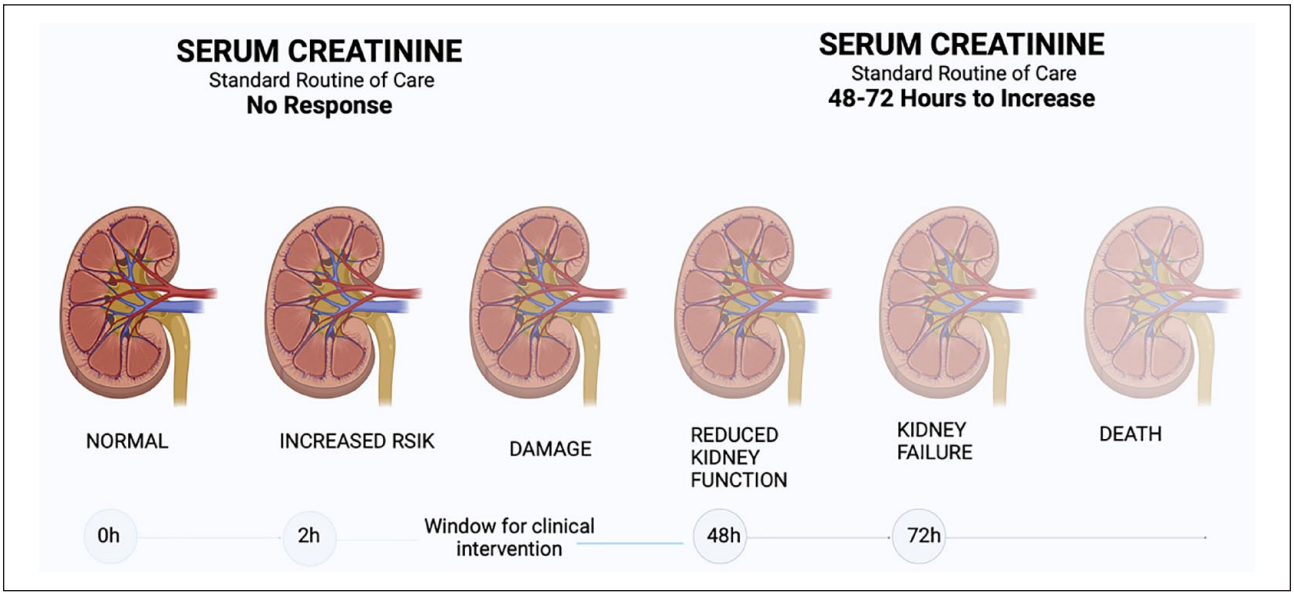

Figure 2. Timeline of serum creatinine response during kidney injury.
Schematic representation of serum creatinine response after kidney injury. Adapted From *neutrophil gelatinase-associated lipoprotein*, by BioPorto, 2022, Bioporto. (https://bioporto.com/ngal/). Copyright 2020 by BioPorto. Created with BioRender.com.

prevent the development of chronic renal failure.[27] Studies have shown that implementation of early AKI prevention and intervention strategies is essential in reducing mortality.[28] With early identification and abrupt treatment of pharmacological traits that can trigger AKI, mortality and morbidity can be decreased because of the direct correlation between the timing of renal injury and mortality.[10]

Hence, based on the above evidence, there is an urgent need to identify and discover novel biomarkers of nephrology conditions to improve patient outcomes and assist in caring for patients at risk of kidney disease.

Kidney biomarkers

AKI currently relies on clinical assessment of kidney structures, such as the glomerulus, which is a one-dimensional paradigm and limits the diagnosis/treatment of AKI. For early and accurate diagnosis/prognosis of AKI, it is necessary to have a biomarker that is capable of allowing for early prediction to prevent the progression of the disease. To address these limitations, the utilization of biomarkers is vital in assessing normal biological and pathogenic processes and pharmacological reactions to therapeutic implications. In earlier studies, the focus was on measuring and evaluating kidney disease using physical examination and findings of interstitial edema or ascites. It has been determined that this marker was not specific in indicating kidney failure but more suitable for identifying congestive heart failure and cirrhosis. As time progressed, biomarkers of nephrology included examinations of urine sediment, shadowed by assessing blood urea nitrogen and SCr concentrations. However, due to the many limitations and futility of these current markers, as mentioned previously, there has been extensive growth in the discovery of novel biomarkers that are more specific, sensitive, and prognostically accurate in helping to assess, and treat patients earlier who are at risk of developing kidney disease and to prevent disease progression. To have a successful impact on the diagnosis of AKI, novel biomarkers must include ideal features such as recognizing the cause of AKI, providing useful prognosis information, monitoring the success of therapeutic interventions, and being able to identify the anatomic location of the injury, for instance, tubular, glomerular, vascular, or interstitial.[9]

Emerging biomarkers for early AKI diagnosis

As the pathology of AKI continues to be extensively studied, there has been the discovery of more effective and early biomarkers such as cystatin C (CysC), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipoprotein (NGAL), tissue inhibitor of metalloproteinase 2 (TIMP-2), and insulin-like-growth-factor-binding protein 7 (IGFBP-7) (Figure 3).

CysC is a cysteine protease inhibitor freely filtered within the glomerulus and reabsorbed by the proximal tubular cells. It is solely cleared by the kidney, making it an accurate marker of glomerular filtration rate compared to creatinine.[29] Furthermore, it is also not affected by age, muscle mass, or sex like creatinine.[30] In addition, CysC can recognize subclinical AKI and indicate tubular injury because it can predict AKI within 24–48 h before any rise in SCr levels.[31]

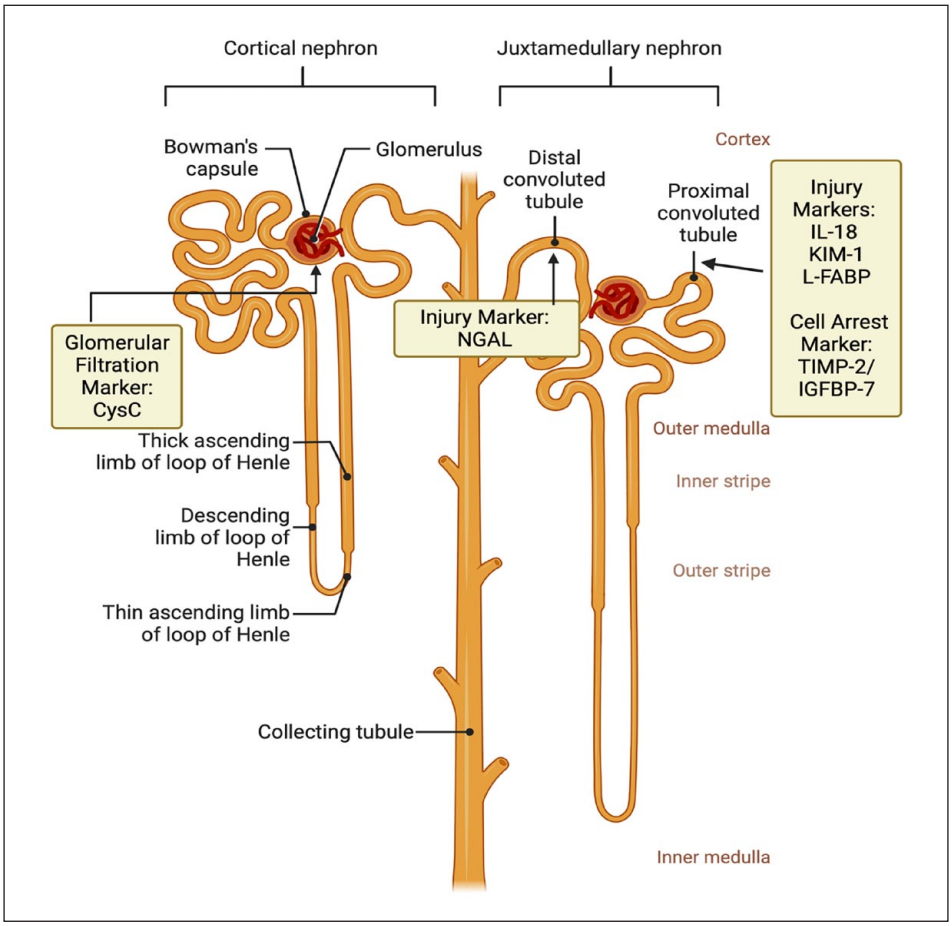

Figure 3. Structural acute kidney injury biomarkers.
Structural biomarkers of acute kidney injury are illustrated according to their anatomic location and mechanism. Created with BioRender.com.

IL-18 is a cytokine synthesized by cells such as monocytes, macrophages, and proximal tubular epithelial cells. Once it is activated in the proximal tubule cells, it can be present in urine after cleavage by caspase-1 and be quantified by Enzyme-linked immunosorbent assay (ELISA) methods.[32] It is expressed as early as 12 h before clinical AKI. In a study with human subjects, urinary IL-18 levels increased significantly after acute tubular necrosis in comparison to healthy subjects.[33] IL-18 combined with other biomarkers improves its performance accuracy in predicting AKI.[34]

KIM-1, however, has the potential to be an early biomarker of AKI because it is not expressed at high levels in healthy kidney epithelial cells. KIM-1 is expressed at high concentration in the proximal tubule cells of the kidney after 2 h of insult.[27] Studies have shown that an increase in KIM-1 is associated with a decrease in GFR.[35] KIM-1 is found in the urine after ischemic insult and is steady for a long period of time.[36] KIM-1 has clinical promise because it can detect early tubular injury through noninvasive methods.[37] It has shown the best performance capability in ischemic acute tubular necrosis. KIM-1 has been approved in the US by Food and Drug Administration (FDA) for preclinical drug development.[34]

L-FABP is also expressed in the proximal tubules and is part of a family of cytosolic proteins active in endogenous cytoprotection by decreasing oxidative stress in ischemia-reperfusion. It can be expressed within 0–2 h of kidney injury.[34] An elevation in urine L-FABP concentrations correlates with the stress of proximal tubular cells.[38] In the critical care setting, urinary L-FABP can predict AKI with an area under the curve of 0.75.[39]

NGAL is expressed at low levels in several cell types, including the lung, kidney, and prostate.[31] NGAL is one of the most promising biomarkers of early AKI diagnosis because it is reabsorbed by the proximal tubules and released by damaged distal tubules during acute kidney insult.[40] NGAL levels can rise within 3 h after tubular injury and usually peak between 6 and 12 h based on the severity of the injury.[41] Urine NGAL has been shown to detect renal injury in the initial phase in children with non-steroidal anti-inflammatory drugs (NSAID)-mediated renal tubular injury. Continuous monitoring of NGAL in children using NSAID allows physicians to detect subclinical AKI and its progression since a rise in NGAL levels would allow treatment to prevent AKI and functional impairment.[42] New emerging methods to detect NGAL includes electrochemical immunosensor, SPR

biosensor and Raman spectroscopy. The advantages of these methods are simplicity, short detection time, high sensitivity and decrease in false positive results which are ideal characteristics of a biomarker.[27]

TIMP-2/IGFBP-7 are cell cycle arrest proteins presented in renal tubular cells during cell stress. It was one of the first emerging biomarkers of AKI to be approved by the FDA in the US for urinary detection. Multiple studies have confirmed the use of TIMP-2/IGFBP-7 for diagnosis of AKI stage 2 or 3 within 12 h of admission in critically ill patients.[43] These studies led to the 2014 FDA approval of the NephroCheck test, which is a fluorescence lateral flow immunoassay of the urinary concentration of TIMP-2 and IGFBP-7. The test results have identified these two proteins (TIMP-2 and IGFBP-7) as a risk score for AKI. The test has a fast turnaround time of 20 min.[44] However, the test has some limitations, including cost, interference with bilirubin in the urine over 72 mg/dL, and poor specificity at a cutoff value of 0.3 ng/mL.[34]

Overall, progress has been made in identifying new AKI biomarkers; however, they have not been widely accepted in clinical practice. At the 23rd ADQI Consensus Conference, it was recommended that structural and functional markers be combined with clinical assessment to enhance AKI diagnostic accuracy, distinguishing between AKI etiology and evaluating AKI severity. The discovery of structural kidney injury markers has made it possible for a more reliable characterization of pathophysiology, injury location, and prognosis, which are all vital to improve patient outcomes.[45] Following the discovery of novel biomarkers, several steps and processes must occur for a biomarker to be used for diagnostic purposes, including characterization and validation.

Discovery and development of biomarker

Biomarkers are indicators of normal and abnormal biological responses that are used in screening, diagnosis, prognosis, and risk assessment of AKI. Hence, for the development of biomarkers, the following attributes must be present: it should be measured fast with higher specificity and sensitivity, the cost of tests should be low, and it should have a faster turnaround time. At present, seven types of AKI biomarkers are available, namely, diagnostics, monitoring, pharmacodynamics/response, predictive, prognostics, safety, and susceptibility/risk, which are applied at different stages of the disease (Table 2). For instance, risk stratification biomarkers are used to distinguish patients who are at greater risk of developing the disease and are necessary to monitor the progression of the disease; disease screening and detection markers are used to recognize the condition before symptoms are apparent, diagnostic biomarkers are used to identify the presence of a disease while prognosis biomarkers provide general information on the anticipated clinical results without taking the treatment and therapy into consideration. Finally, predictive biomarkers are used for treatment selections to make decisions on the clinical outcome, and monitoring biomarkers are used to follow up for the improvement of the treatment process.[46]

Biomarker discovery and development are vital processes in diagnostic applications. Before a biomarker can be used in the clinic for diagnostic purposes, it must pass through a series of developmental processes such as discovery, analytical validation, clinical qualification, and utilization. The discovery stage is where candidate biomarkers are identified before preceding the analytical validation phase.[56] At this stage, evaluating the relationship between the biomarker and the disease status, demographics, and clinical characteristics is important because it reveals the design needed for future validation studies. Characteristics such as sensitivity, specificity, positive and negative predictive values, receiver operating characteristics, calibration, and clinical validity should be assessed when evaluating a biomarker's performance. During the analytical validation phase, the performance metrics of the biomarker are evaluated to confirm that the test is reliable, reproducible, and demonstrates accuracy, precision, sensitivity, and specificity for the intended use, meaning that the biomarker is capable of providing consistent results in comparison to the unknown true value.[46,56] The next phase is the clinical qualification/validation, which is important in connecting the biological and clinical endpoints and describing the validity and reliability of the biomarker. Lastly, there is the utilization phase. This phase is needed to show how beneficial the test is in patient care.[56]

Conclusion

AKI is a prevalent illness among patients diagnosed with sepsis, heart conditions, and diabetes. It is a serious medical problem in all clinical departments, including emergency departments and intensive care units, with a high morbidity and mortality rate.[16] Numerous studies have shown that current markers SCr, urine output, and GFR are ineffective in managing and monitoring structural injury of the kidney and support the need for novel AKI biomarkers discovery and development. KDIGO diagnostic criteria are very cumbersome and give inaccurate results that limit the diagnosis and treatment of AKI. At present, AKI biomarkers lack sensitivity and specificity in measuring and evaluating the progression of the disease, thus hindering therapeutic interventions.[31] The current article has focused on identifying the key features that make biomarkers ideal for diagnostic use, such as distinguishing the severity of the disease and the anatomic location of the injury.

The need to discover and validate markers of kidney injury has become more apparent, and many biomarkers have been explored for their predictive value and unique

Table 2. Recent discovery biomarkers.

Biomarker	Subtypes	Significance
CYS-C	Predictive[47]	Outperforms SCr in emergency department, tubular Injury marker, Predictive 24–48 h before SCr *Sample Type*: Serum
IL-18	Predictive[48]	Elevated within 12 h of injury, an early predictive marker of AKI after cardiac surgery. *Sample Type*: Urine
KIM-1	Diagnostics, prognostic, monitoring[34,37]	Expressed in proximal tubule cells within 2 h of injury, correlates with a decline in GFR, and Early AKI detection in patients with COVID, FDA Approved. *Sample Type*: Urine, Plasma
L-FABP	Diagnostics, predictive, prognostics[49–51]	An effective biomarker for predicting AKI during the first seven days of hospitalization is a renal tubular injury biomarker, elevated with 0–2 h of injury. *Sample Type*: Urine
NGAL	Diagnostics, predictive prognostics[52,53]	Can predict AKI occurrence 72 h before ICU admission, Levels in the blood increase 2–6 h after AKI, and Distinguish between the type of AKI in cirrhosis. *Sample Type*: Urine, Plasma, and Serum
TIMP-2/ IGFBP-7	Predictive, susceptibility/ risk[54,55]	FDA Approved, Useful in early diagnosis of high-risk patients, Highly Sensitive, Predictive as early as 12 h of AKI *Sample Type*: Urine

IGFBP-7: insulin-like growth factor-binding protein 7; IL-18: interleukin 18; KIM-1: kidney injury molecule-1; L-FABP: liver fatty acid binding protein; NGAL: neutrophil gelatinase-associated lipocalin; TIMP-2: tissue inhibitor of metalloproteinases-2.
Biomarker Subtype Classification of recently discovered AKI biomarkers.

characteristics in early diagnosis of AKI. For instance, for patients undergoing cardiac surgery, NGAL is an effective marker since it is upregulated earlier than conventional markers, including SCr.[57] Moreover, urinary KIM-1 is an excellent predictor of AKI in adult patients with high sensitivity and specificity,[58] and CysC is more valuable in predicting AKI after a major surgery.[59] Given the critical characteristics of these biomarkers and the value they add to early diagnosis of AKI, it is reasonable to expect that these markers could be used as therapeutic targets and early intervention. Thus, future research should concentrate on enhancing the understanding of their role in the sequence of renal stress and disease.

The recommendations of ideal biomarker characteristics are not new; however, they are imperative in improving therapeutic interventions and patient outcomes of renal diseases. Several novel biomarkers have been discovered and validated, but none of these markers are currently specific to AKI. Therefore, it is still challenging to introduce these AKI biomarkers into the medical practice. However, some biomarkers, such as NGAL can predict AKI in patients needed for renal replacement therapy,[60] IL-18 in patients with sepsis,[61] and L-FABP in patients with sepsis and open heart surgery.[62] These data suggest that the specificity of the biomarkers for predicting AKI differs with the different clinical situations. Thus a broad understanding of the biomarker's unique characteristics and AKI phenotype based on pathophysiology is needed.

This manuscript focused on the disadvantages of conventional biomarkers and the challenges of implementing functional biomarkers of AKI. In addition, this review included and discussed emerging structural biomarkers but was limited in describing or discussing novel technologies, such as machine learning and nanodrugs, that are currently being studied to alleviate kidney injury. However, recent review articles have looked at these tools to improve AKI therapeutic intervention.[27,63]

In conclusion, as the research advances in the development of new biomarkers, drugs, and technology, enhancing the understating of AKI biomarkers and AKI phenotype will help improve test performance and establish specific treatment regimens to improve patient prognosis and advance patient care.

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