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Advances in the diagnosis of early biomarkers for acute kidney injury: a literature review

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Abstract

Acute kidney injury (AKI) is a critical condition with diverse manifestations and variable outcomes. Its diagnosis traditionally relies on delayed indicators such as serum creatinine and urine output, making early detection challenging. Early identification is essential to improving patient outcomes, driving the need for novel biomarkers. Recent advancements have identified promising biomarkers across various biological processes. Tubular injury markers, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP), offer insights into early tubular damage. Inflammatory and repair-associated biomarkers, such as interleukin-18 (IL-18), monocyte chemotactic protein-1 (MCP-1), osteopontin (OPN), and C-C motif chemokine ligand 14 (CCL14), reflect ongoing injury and recovery processes. Additionally, stress and repair markers like tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7), alongside filtration markers such as cystatin C (CysC) and proenkephalin (PenKid®) e.tal, further enhance diagnostic precision. Oxidative stress-related markers, including Superoxide Dismutase 1 (SOD1), also contribute valuable information. Emerging candidates, such as microRNAs, soluble urokinase plasminogen activator receptor (SuPAR), and chitinase-3-like protein 1 (CHI3L1), hold substantial promise for AKI detection and prognosis. This review summarizes the progress in AKI biomarker research, highlighting their clinical utility and exploring their potential to refine early diagnosis and management strategies. These findings offer a new perspective for integrating novel biomarkers into routine clinical practice, ultimately improving AKI care.

Clinical trial number

Not applicable.

Keywords Acute kidney injury, Biomarkers, Early diagnosis, Prognostic

Introduction

Acute kidney injury (AKI) is a heterogeneous group of conditions, typically occurring in the context of acute or chronic illness, characterized by a rapid decline in glomerular filtration rate (GFR), accompanied by an increase in serum creatinine concentration or a decrease in urine output [1, 2]. The term "acute" refers to kidney dysfunction occurring within hours to days, while "kidney injury" implies a potentially reversible condition that, if not promptly addressed, may progress to acute kidney disease (AKD) and even chronic kidney disease (CKD) [3, 4]. AKI affects 15–20% of hospitalized patients [5],

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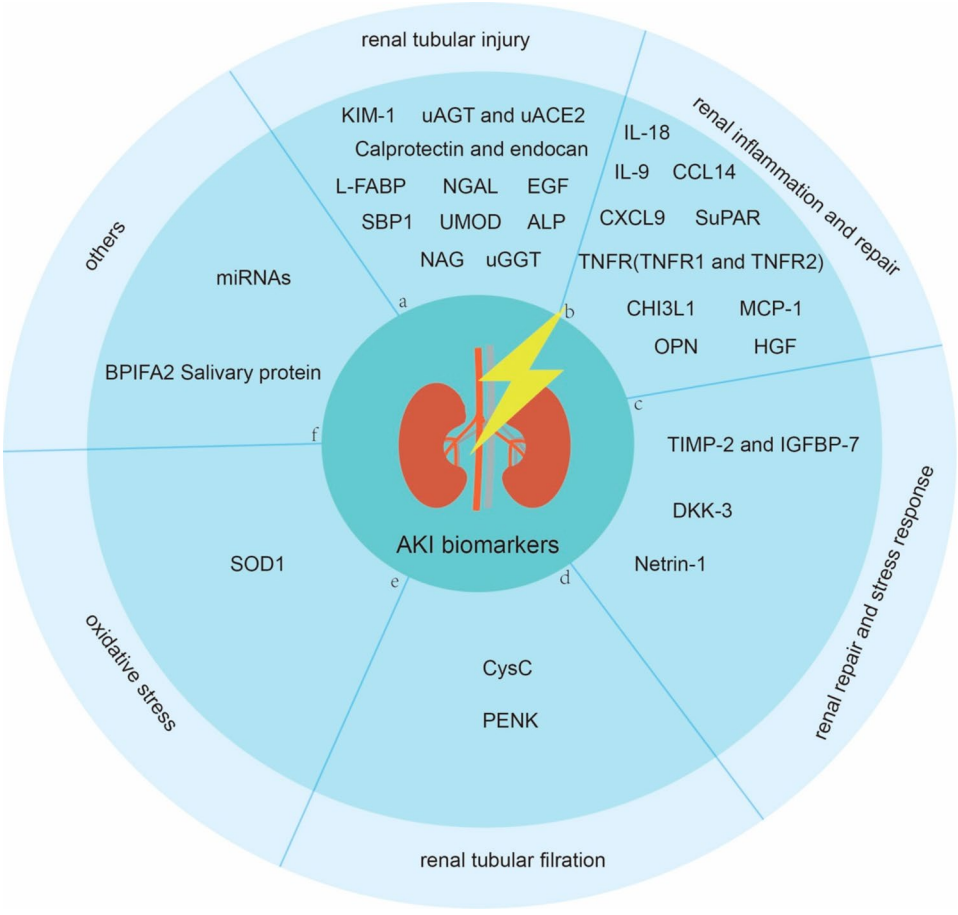

Fig. 1 Various types of AKI biomarkers. This figure categorizes biomarkers into six functional groups: biomarkers of renal tubular injury, renal inflammation, repair and stress response, tubular filtration, oxidative stress, and other mechanisms. This figure was created using Adobe Illustrator 2020

doubling the risk of in-hospital mortality and increasing the risk of CKD by fourfold [6]. Current clinical diagnosis relies on serum creatinine levels, but its lagging nature limits the early diagnosis and treatment of AKI. As a marker of GFR, creatinine only increases when there is a significant drop in GFR or substantial parenchymal damage, and it does not reflect specific pathological processes [5]. AKI primarily affects the tubules, with changes in GFR typically occurring only after tubular damage has progressed. The absence of changes in creatinine levels may lead to false reassurance, resulting in inappropriate medication dosing or delays in discontinuing nephrotoxic agents, thereby increasing the risk of worsening kidney injury [7].

Biomarkers are defined and categorized according to the BEST (Biomarkers, EndpointS, and other Tools) resource from the joint task force of the FDA and NIH, covering functions such as diagnosis, monitoring, prognosis, and prediction, and guiding the application of clinical and surrogate endpoint biomarkers [8]. Ideally, biomarkers should be validated in multicenter and prospective cohorts, and tested in clinical trials for their impact on patient outcomes [9]. As many researchers have advocated, in AKI, an ideal biomarker may not replace serum creatinine (SCr) and urine output but should be considered of additional value [10, 11]. In recent years, biomarkers for tubular injury, inflammation and repair, renal filtration, and oxidative stress have shown significant potential in the early detection and prognosis of AKI (Fig. 1). However, their clinical implementation faces challenges in terms of technology and validation, requiring large-scale studies to confirm their effectiveness. This review summarizes the current state of early diagnostic and prognostic biomarkers for AKI, exploring their prospects in clinical practice and providing guidance to improve the diagnosis and treatment of AKI.

Current diagnostic methods for AKI and their limitations

The diagnostic criteria for AKI primarily include the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease), AKIN (Acute Kidney Injury Network), and KDIGO (kidney disease: Improving Global Outcomes)

standards, all of which emphasize the importance of SCr. Common adjunctive diagnostic methods also include urine output monitoring, imaging tests, and assessments of electrolytes and acid-base balance. In clinical practice, the KDIGO standard is widely used as it combines the advantages of the RIFLE and AKIN criteria, providing a more comprehensive basis for the diagnosis of AKI.

Serum creatinine

SCr is the most used diagnostic tool for acute changes in kidney function. The 2012 KDIGO guidelines recommend the following criteria: [1] an increase in SCr of ≥0.3 mg/mL (≥26.5 μmol/L) within 48 h; [2] a SCr increase of more than 1.5 times baseline within the past 7 days; [3] urine output ≤0.5 mL/(kg·h) for more than 6 h [12].

Due to the long half-life of SCr and kidney functional reserve, changes in SCr are not significant during early kidney injury and may not reflect pathological changes in a timely manner. SCr values are influenced by factors such as muscle mass, metabolism, liver function, diet, hydration, and exogenous creatinine intake, and can also be affected by physiological and analytical variability. Drugs (such as cimetidine and trimethoprim) that inhibit tubular secretion or blood concentration (such as diuretics) may cause false elevation, while changes during pregnancy can also affect SCr levels [13]. Additionally, prerenal, intrinsic, and postrenal AKI can all lead to an increase in SCr, requiring a comprehensive interpretation in conjunction with the specific cause. Faster testing methods, such as creatinine clearance over 2–4 h, dynamic estimated GFR (kinetic eGFR), or plasma clearance of renal clearance-dependent compounds (such as iohexol), though not yet widely adopted in clinical practice, have been proposed as alternative tools to SCr testing [14].

Urine output monitoring

Urine output is one of the standard tools for diagnosing AKI. Oliguria (<0.5 mL/kg/h) or anuria (<50 mL/day) are early clinical signs of AKI [15, 16]. In 2012, the KDIGO guidelines proposed that a urine output of ≤0.5 mL/(kg·h) within 6 h can diagnose AKI [1]. Although the reliability of oliguria as a renal function marker is debated, studies have shown it is closely associated with worse prognosis [17, 18].

In AKI, changes in urine output alone may not accurately reflect the severity of kidney injury. Prerenal AKI typically presents with a significant reduction in urine output, whereas in renal AKI, particularly in cases of acute tubular necrosis (ATN), urine output may remain normal. Additionally, transient oliguria can be a physiological phenomenon and can be modulated with diuretics, but measurement errors can still occur even with a catheter [13]. In patients with chronic underlying diseases, urine output tends to decrease more gradually, and recovery is more complex, further complicating the interpretation.

Imaging and electrolyte tests

Imaging and laboratory tests play a crucial role in identifying the cause of AKI and evaluating complications. Common imaging techniques include X-ray, ultrasound, CT, and MRI. X-ray can detect stones and calcification, while ultrasound is useful for evaluating kidney structure and urinary tract obstruction, especially in diagnosing postrenal AKI [19]. CT provides detailed anatomical images, but contrast agents may exacerbate kidney damage, so caution is needed. MRI has no radiation and can be used in complex cases or when other imaging methods are inconclusive.

Laboratory tests focus on electrolyte and acid-base imbalances, such as hyperkalemia, hyponatremia, and hyperphosphatemia. Blood electrolyte testing can guide treatment, but it should be considered in conjunction with other clinical information for a comprehensive assessment.

Classification and research progress of AKI biomarkers

Biomarkers of renal tubular injury

Neutrophil gelatinase-associated Lipocalin (NGAL)

NGAL is broadly expressed in various organs, including the kidneys, with low basal levels under normal conditions but significant upregulation following tubular injury. As an early biomarker for AKI, plasma and urinary NGAL have demonstrated clinical value in contexts such as cardiopulmonary bypass surgery, kidney transplantation, contrast agent administration, and ICU settings [20]. A meta-analysis revealed that urinary and plasma NGAL have an AUC of 0.75–0.86 for predicting severe AKI and dialysis-requiring AKI (AKI-D). However, its limited sensitivity necessitates further validation of thresholds, such as plasma NGAL >546 ng/mL [21]. Urinary NGAL levels are significantly higher in patients with ATN than those with hepatorenal syndrome (HRS) or prerenal azotemia (PRA), effectively predicting mortality and serving as a prognostic marker in AKI associated with cirrhosis [22].

Additionally, preoperative serum NGAL has shown strong predictive performance for AKI after cardiac surgery, with sensitivity surpassing that of troponin I and approaching that of creatinine, though its specificity remains low. Studies suggest that preoperative serum NGAL, eGFR, and hypertension are risk factors for AKI and adverse outcomes [23]. Similarly, urinary NGAL effectively predicts 30-day and 3-month mortality in pediatric AKI patients (AUCs of 0.79 and 0.81,

respectively), outperforming pediatric RIFLE (pRIFLE) staging, eGFR, or creatinine. In contrast, urinary calprotectin and KIM-1 perform less well in mortality prediction but show moderate utility in forecasting the need for RRT (both AUCs around 0.7) [24]. However, the utility of NGAL is limited in critically ill patients due to its complexity and unpredictable release during systemic inflammation and comorbid conditions [20].

Kidney injury molecule-1 (KIM-1)

KIM-1 is secreted by renal proximal tubular epithelial cells and exhibits minimal expression in normal kidney tissue. However, its levels rise significantly following nephrotoxic drug exposure or ischemic injury. Studies have demonstrated that urinary KIM-1 (uKIM-1) can distinguish transient AKI from persistent kidney injury and predict long-term renal outcomes, with a ROC curve AUC of 0.703, sensitivity of 78.4%, and specificity of 60.8%; levels exceeding 2.37 ng/mg are associated with worse prognoses [25]. A systematic review reported uKIM-1's diagnostic sensitivity and specificity for AKI as 74% and 84%, respectively, with an AUC of 0.6220 [26]. However, its widespread clinical use requires further validation. A meta-analysis highlighted uKIM-1's predictive value for contrast-induced AKI (CI-AKI), showing an AUC of 0.88 with sensitivity and specificity of 84% and 78%, respectively, supporting its utility as an effective biomarker for CI-AKI [27]. Nevertheless, certain heterogeneities in its application remain.

N-acetyl-β-D-glucosaminidase (NAG)

NAG is an intracellular lysosomal enzyme most abundant in renal proximal tubules and found widely in various tissues, body fluids, and cells. Changes in NAG activity are closely associated with certain pathological conditions and make it a commonly used biomarker for tubular injury. Unlike SCr, which cannot accurately reflect the extent of tubular damage, urinary NAG (uNAG) serves as a valuable tool for a more comprehensive assessment of the nature and severity of kidney injury. A study on patients undergoing total aortic arch replacement (TAAR) demonstrated the significant predictive capability of uNAG as a biomarker for AKI, with an AUC-ROC of 0.802. In random forest analysis, uNAG ranked second, providing critical support for the early identification of AKI following TAAR [28].

Liver-type fatty acid-binding protein (L-FABP)

L-FABP, a 14-kDa fatty acid-binding protein, is upregulated in acute liver injury, diabetic nephropathy, and AKI, demonstrating potential in binding free fatty acids and mitigating kidney injury [29, 30]. The human form (hL-FABP) is widely expressed in both normal and diseased kidneys, highlighting its diagnostic and protective roles [29]. As a biomarker for renal diseases, hL-FABP shows excellent predictive and diagnostic value in AKI and CKD. It has also been employed for early diagnosis of hepatorenal injury, with a diagnostic cutoff of 334.3 ng/mL (sensitivity 90%, specificity 78%) [31]. Furthermore, studies indicate that L-FABP significantly improves diagnostic accuracy for contrast-induced AKI by nearly threefold (OR = 2.9). Its clinical utility is especially pronounced pre- and intraoperatively, offering guidance on interventions like volume expansion and avoiding nephrotoxic agents [32]. Similarly, urinary L-FABP rises significantly within six hours of cisplatin treatment, effectively predicting AKI. Notably, this elevation precedes changes in serum creatinine levels [33].

Selenium binding protein 1 (SBP1)

SBP1 is a selenium-associated protein involved in protein transport, degradation, sulfur metabolism, and regulation of hypoxia-inducible factors. It has been identified as a urinary biomarker for early kidney injury. Studies have shown that urinary SBP1 levels significantly increase in the early stages of AKI, displaying higher sensitivity than traditional markers like NGAL and TIMP-2 [34]. Under normal conditions, SBP1 is expressed in proximal tubular cells, but its expression is notably downregulated during AKI. This reduction correlates with decreased GPX4 and increased ACSL4, key markers in oxidative stress and lipid peroxidation. Overexpression of SBP1 alleviates oxidative stress and mitochondrial damage, promoting cell survival. Additionally, selenium supplementation has been shown to restore GPX4 levels, suggesting a synergistic therapeutic potential of SBP1 and selenium in AKI management [35].

Urinary angiotensinogen (uAGT) and urinary angiotensin-converting enzyme 2 (uACE2)

In AKI, activation of the renin-angiotensin-aldosterone system (RAAS) leads to increased levels of angiotensin II (Ang II), driving the progression of AKI. Angiotensinogen (AGT), an upstream molecule in the RAAS, is a stable marker in urine. Compared to Ang II, it more effectively evaluates RAAS activity and helps predict CKD progression. Animal studies have shown a significant increase in urine AGT early in ischemic AKI, contributing to disease progression [34]. Clinical data demonstrate that urine AGT outperforms urine NGAL in predicting AKI in patients with acute decompensated heart failure (AUC = 0.84) and independently predicts one-year mortality and rehospitalization after discharge. Urine AGT also excels in predicting AKI progression (AUC = 0.78) and mortality (AUC = 0.85) and can effectively predict the risk of stage III AKI or death after cardiac surgery using the AGT/creatinine ratio (AUC = 0.75). AGT holds potential for monitoring kidney function recovery in

ATN patients and predicting AKI to CKD transition [34]. Moreover, urine AGT/creatinine ratio is associated with the severity and prognosis of AKI and positively correlates with serum creatinine levels three months later [36]. Therefore, urine AGT level can serve as a biomarker for assessing AKI severity and prognosis.

Angiotensin-converting enzyme 2 (ACE2) is widely expressed in proximal tubular cells, vascular endothelial and smooth muscle cells, and podocytes [37]. Its urinary activity (uACE2) reflects the upregulation of the non-classical renin-angiotensin system. In critically ill patients, elevated uACE2 activity is significantly associated with a reduced early AKI risk (OR = 0.72, $P < 0.05$) and correlates with AKI progression during ICU stay [38]. Among COVID-19 patients, increased uACE2 levels are strongly associated with a more than threefold higher risk of AKI (OR = 3.05, $P = 0.017$), accompanied by aminoaciduria and ACE2 loss in renal tubules [39]. Research on diabetic kidney disease (DKD) indicates that patients with higher plasma ACE2 levels exhibit more stable renal function and improved albuminuria outcomes [37]. These findings suggest that uACE2 and plasma ACE2 hold potential as biomarkers for assessing AKI and DKD risk.

Calprotectin and endocan

Calprotectin is an immune regulatory protein formed by two calcium-binding proteins, S100A8 and S100A9, primarily found in neutrophils. It counteracts oxidative stress and neutralizes reactive oxygen species produced during inflammation [40]. Endocan is a dermatan sulfate proteoglycan secreted by endothelial cells, with very low levels in normal serum. It plays a key role in inflammation regulation, inhibiting leukocyte adhesion, migration, and recruitment [41]. Studies have shown that calprotectin in urine reflects tubular injury and helps differentiate pre-renal from renal AKI. Serum endocan levels are associated with endothelial injury and can distinguish between tubular and glomerular/vascular damage [32]. Plasma calprotectin and NGAL levels are significantly elevated in AKI patients, showing high predictive ability, suggesting they are potential early diagnostic biomarkers for AKI in Acute Coronary Syndrome (ACS) patients [42]. Urinary calprotectin effectively differentiates between intrinsic and prerenal AKI and serves as a sensitive early biomarker for intrinsic AKI [43]. Furthermore, studies have also found that urinary calprotectin is a sensitive early biomarker for intrinsic AKI, with a sensitivity of 92.5% and specificity of 92.8%, outperforming serum creatinine and suitable for rapid screening in pediatric intensive care units [44].

Uromodulin (UMOD)

UMOD, also known as Tamm-Horsfall protein (THP), is primarily expressed by the renal tubular epithelial cells of the thick ascending limb of Henle's loop and is one of the most abundant proteins in the urine of healthy individuals. Studies have found that lower preoperative UMOD-to-creatinine ratio is associated with an increased risk of postoperative AKI and elevated peak serum creatinine levels [45]. In another study of children undergoing cardiopulmonary bypass (CPB), low preoperative urinary UMOD (uUMOD) levels significantly increased the risk of developing postoperative AKI, with an AKI incidence of 92% in the low uUMOD group compared to 8% in the high uUMOD group. uUMOD strongly predicted postoperative AKI, with an AUC of 0.90, indicating its potential as an early warning marker in CPB surgeries [46]. Additionally, research suggests that UMOD may provide potential protective effects against proximal renal tubular injury by inhibiting the chemotaxis of monocytes and macrophages [7].

Epidermal growth factor (EGF)

The role of EGF and its receptor in AKI has received significant attention. EGF activates signal transduction pathways by binding to EGFR, regulating cell proliferation, apoptosis, and differentiation. In the kidneys, EGF is primarily expressed in renal tubular epithelial cells and temporarily decreases after ischemia-reperfusion injury. Clinical studies have shown that EGF levels in the urine of AKI patients are significantly lower than in healthy controls, and exogenous EGF can promote DNA replication and renal function recovery. While EGFR activation is critical for renal repair, prolonged activation may lead to renal fibrosis [47], making the EGF/EGFR signaling pathway a target for AKI treatment that requires cautious use. Urinary EGF (uEGF), as a biomarker of renal tubular function, helps assess the risk of AKI progression to CKD. A multicenter prospective study found that the uEGF/creatinine ratio was significantly associated with the risk of major adverse kidney events (MAKE), and changes in uEGF/Cr could predict the onset of kidney failure [48]. Additionally, in 865 adults undergoing heart surgery, higher post-operative EGF levels were weakly correlated with CKD progression, whereas MCP-1 levels were significantly associated with CKD progression. Single-cell RNA sequencing further revealed that the changes in EGF and MCP-1 levels reflect molecular processes of renal tubular injury, suggesting that these biomarkers could serve as non-invasive indicators for early identification of CKD risk and offer new opportunities for intervention [49].

Alkaline phosphatase (ALP) and urinary γ-glutamyl transferase (uGGT)

ALP is an enzyme widely found in the kidneys, intestines, and liver, with detoxifying effects through dephosphorylation of endotoxins and pro-inflammatory substances. ALP levels decrease significantly during ischemia and are associated with AKI [50]. γ-glutamyl transferase (GGT) is an enzyme in renal tubules that leaks into the urine when the tubules are damaged. Although GGT activity decreases over time, it can still be measured using the same equipment as serum GGT [51]. Studies show that urinary alkaline phosphatase (uALP/uCr) is a more suitable biomarker for AKI than γ-glutamyl transferase (uGGT/uCr), although both have low sensitivity and specificity. uALP/uCr and uGGT/uCr can serve as auxiliary biomarkers, and selecting an appropriate high-specificity threshold helps in detecting AKI in dogs [52]. One study found that uGGT performs well in distinguishing between dogs without AKI and those with stage 1 AKI, making it an effective biomarker for stage 1 AKI. Additionally, molecularly activated urine report probes (MURs) have been developed to specifically detect urinary biomarkers like GGT, AAP, and NAG, which detect drug-induced acute and chronic kidney injury earlier and more accurately than traditional methods [53].

Biomarkers of renal inflammation and repair

Interleukin-18 (IL-18)

IL-18, a pro-inflammatory cytokine secreted by proximal tubules, serves as an early biomarker of AKI in patients undergoing kidney transplantation, acute respiratory distress syndrome, and cardiopulmonary bypass surgery. A systematic review and meta-analysis reported that urinary IL-18 (uIL-18) has a sensitivity of 64%, specificity of 77%, and an AUC of 0.78, indicating moderate diagnostic utility, with better performance in pediatric patients compared to adults (AUC: 0.81 vs. 0.77) [54]. In a study of 2,796 patients, uIL-18 demonstrated a diagnostic odds ratio (DOR) of 5.11, with 51% sensitivity, 79% specificity, and an AUC of 0.77. It was particularly effective in children (< 18 years old) and for early detection (< 12 h), where DORs were 7.51 and 8.18, respectively [55]. Moreover, in pediatric sepsis, a uIL-18 cutoff value of 3.868 ng/ml yielded a sensitivity of 92.50% and a specificity of 91.78% for predicting AKI, with a relative risk of 20.08 (95% CI, 6.593–61.142) [56]. Compared to other biomarkers like urinary KIM-1 and IGFBP-7, uIL-18 exhibited superior predictive accuracy, establishing itself as a reliable early biomarker for sepsis-associated AKI.

Interleukin-9 (IL-9)

Interleukin-9 (IL-9) is a small glycoprotein belonging to the common gamma chain (γc) cytokine family, primarily secreted by CD4 + T helper cells, type 2 innate lymphoid cells (ILC2s), and mast cells [57]. Urinary IL-9 and TNF-α, as diagnostic markers for AIN, significantly improve the performance of diagnostic models, increasing the area under the curve (AUC) from 0.73 to 0.84 [58]. Furthermore, their combined use further optimized the diagnostic accuracy for AIN (AUC increased from 0.62 to 0.84) [59]. Additionally, IL-9 plays an important role in the prognostic evaluation of AIN patients, especially in those who are not treated with corticosteroids, where IL-9 levels are closely correlated with renal function decline. In patients with higher IL-9 levels, corticosteroid treatment significantly improves renal function [60]. These markers provide powerful tools for clinical practice beyond traditional diagnostic methods, helping to differentiate AIN from other acute kidney diseases and offering insights for personalized treatment.

Tumor necrosis factor receptors (TNFR)

TNFR, including TNFR-1 and TNFR-2, are receptors for Tumor Necrosis Factor (TNF-α), and their roles in kidney diseases have been studied. For example, elevated serum soluble TNFR-1 (sTNFR-1) concentrations have been linked to accelerated decline in estimated glomerular filtration rate (eGFR) over 10 years in various ethnic groups, suggesting that sTNFR-1 could serve as a biomarker for kidney disease progression, independent of known risk factors [61]. Additionally, urinary TNF-α is a key diagnostic marker for acute interstitial nephritis (AIN), and its combined use with IL-9 has significantly improved diagnostic model performance [58, 59]. Another study found that high plasma concentrations of KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, and YKL-40 were associated with an increased risk of diabetic kidney disease progression, particularly TNFR-2, which was most closely linked to renal disease progression [62]. Similarly, urinary IGFBP-3, TNFR-2, and fractalkine (FKN) were found to effectively predict renal structural pathology in both AKI and CKD stages, offering potential biomarkers for early prediction of CKD after AKI [63].

C-C motif chemokine ligand 14 (CCL14)

C-C Motif Chemokine Ligand 14 (CCL14) is a C-C chemokine primarily involved in immune regulation and inflammatory responses. Studies have shown that elevated urinary CCL14 concentrations significantly increase the risk of persistent severe AKI, with an AUC of 0.81 (95% CI, 0.72–0.89) for prediction. Higher concentrations are more strongly associated with the risk of kidney replacement therapy (RRT) and/or death within 90 days [64]. A multicenter study identified two key threshold values for urinary CCL14 concentration in predicting persistent severe AKI: ≥1.3 ng/ml with a sensitivity of 91%, useful for screening high-risk patients, and ≥13 ng/ml with a specificity of 93%, accurately identifying

extremely high-risk patients. Patients with concentrations between 1.3 and 13 ng/ml had a 3.82-fold increased risk, while those with >13 ng/ml had a 10.4-fold increased risk [65]. Another study further demonstrated an AUC of 0.83 for CCL14, outperforming biomarkers such as KIM-1, cystatin C, and NGAL, establishing it as the best biomarker for predicting persistent stage III AKI, with significant clinical application value [66].

C-X-C motif chemokine ligand 9 (CXCL9)

C-X-C Motif Chemokine Ligand 9 (CXCL9) is an IFN-γ-induced chemokine that binds to its receptor CXCR-3 to promote the recruitment of lymphocytes to sites of inflammation [67]. Studies have shown that CXCL9 is associated with renal tubular interstitial inflammation, acute kidney transplant rejection, and subclinical rejection. Urinary CXCL9 mRNA and protein levels can effectively diagnose acute rejection (AR) and predict low-risk immune injury, with low urinary CXCL9 protein levels helping to exclude infection/immune-related kidney injury [68]. Additionally, CXCL9 can be used to detect subclinical acute rejection (SCR) in transplanted kidneys [69] and diagnose acute interstitial nephritis (AIN), showing high diagnostic accuracy (AUC = 0.94) [67], outperforming other markers such as TNF-α and IL-9. Overall, CXCL9 significantly improves the diagnostic accuracy for AIN, with its combination with TNF-α and IL-9 demonstrating the best diagnostic performance.

Monocyte chemotactic protein-1 (MCP-1)

Monocyte chemotactic protein-1 (MCP-1), a key member of the CC chemokine family, functions by recruiting monocytes and promoting endothelial cell adhesion. Elevated MCP-1 levels are significantly associated with the risk of AKI and mortality following cardiac surgery (preoperative HR 1.82, postoperative HR 1.95) [70]. In a cisplatin-induced nephrotoxicity model, urinary MCP-1 is also closely linked to AKI. Therefore, MCP-1 may serve as a potential biomarker for identifying high-risk AKI patients. Additionally, higher postoperative urinary MCP-1 levels have been associated with the progression of CKD (adjusted HR 1.10). Single-cell RNA sequencing reveals that changes in MCP-1 reflect the molecular processes underlying tubular injury [49]. MCP-1 can serve as a non-invasive biomarker for predicting CKD risk and providing opportunities for new interventions.

Osteopontin (OPN)

Osteopontin (OPN) is an extracellular matrix protein involved in inflammation and regulates leukocyte activation, migration, differentiation, and cytokine secretion. Studies have shown that urinary OPN is superior to serum creatinine and other markers in early prediction of vancomycin-induced kidney injury (VIKI) and is effective in assessing the degree of kidney injury in combination with KIM-1 [71]. In another study on cisplatin-induced AKI, urinary platinum concentrations were found to be associated with biomarkers such as OPN, which can predict the risk of kidney injury caused by cisplatin [72].

Soluble urokinase plasminogen activator receptor (SuPAR)

SuPAR is a circulating inflammatory mediator with an important role in the diagnosis, evaluation, and prognosis of kidney and inflammatory diseases [73]. By interacting with podocyte integrins, suPAR can cause glomerular dysfunction and plays a key role in the progression of AKI to CKD [74]. Studies show that with each doubling of suPAR levels, the risks for CKD and AKI increase by 1.57 and 2.51 times, respectively (both $P < 0.001$) [75]. Moreover, patients in the highest quartile of suPAR levels have a significantly higher risk of AKI (2.66 times) and a 2.29 times increased risk of AKI or death within 90 days [76]. Experimental models demonstrate that overexpression of suPAR worsens contrast-induced kidney injury, whereas anti-uPAR monoclonal antibodies can improve kidney injury and metabolic changes [76]. Additionally, suPAR is associated with various kidney diseases, such as primary nephrotic syndrome, diabetic nephropathy, and IgA nephropathy. It serves as both a marker of kidney function and injury, reflecting the kidney's inflammation-related characteristics, and shows potential for monitoring and treating kidney transplant recipients.

In Focal Segmental Glomerulosclerosis (FSGS) pathogenesis, suPAR interacts with integrin β6 to promote tubulointerstitial fibrosis via tubular cell-derived versican V1, which activates fibroblasts and enhances extracellular matrix production, making suPAR a potential biomarker and therapeutic target [77]. In vitro studies reveal that suPAR is a key driver of podocyte injury in FSGS, with its blockade significantly reducing damage, supporting its role as a permeability factor [78]. Moreover, research indicates that suPAR induces podocyte injury through αVβ3 integrins and RAGE, triggering downstream effects such as Src phosphorylation, TRPC6 expression, and ROS generation. Blocking suPAR or RAGE effectively mitigates these effects, further confirming suPAR's pathogenic role in FSGS and AKI [79]. While suPAR is proposed as a circulating permeability factor in primary FSGS, its role remains controversial due to conflicting in vivo evidence and unidentified suPAR forms [80].

Chitinase-3-like protein 1 (CHI3L1)

Chitinase-3-like protein 1 (CHI3L1) (also known as YKL-40 or CGP-39) belongs to the glycoside hydrolase family 18. It is produced by neutrophils, monocytes, and macrophages, and is found in macrophages, chondrocytes, synovial cells, and the liver. CHI3L1 is involved in pathogen defense, tissue remodeling, and cellular adaptation.

It has functions in inhibiting oxidative damage and promoting repair and has been confirmed as a biomarker for recovery from AKI. Recent studies have shown that YKL-40 is secreted by kidney macrophages and promotes kidney repair after ischemia/reperfusion injury [81]. Moreover, higher YKL-40 concentrations in the urine of deceased organ donors are associated with lower risk of delayed graft function and better kidney recovery, suggesting that YKL-40 may be used to assess the transplant suitability of donor kidneys [81]. However, the predictive value of YKL-40 in combination with other biomarkers is limited, and its predictive ability for SCr remains weak [82], indicating that further investigation is required to verify its mechanisms and clinical application value.

Hepatocyte growth factor (HGF)

Hepatocyte growth factor (HGF) is a pleiotropic cytokine involved in biological processes such as inflammation and repair. In dialysis patients, elevated levels of HGF are associated with leukocyte activation, which may impact the prognosis of AKI [83]. ANG-3777, a drug that mimics HGF, reduces renal cell apoptosis and promotes repair. In animal models, it alleviates kidney damage caused by ischemia-reperfusion injury and nephrotoxicity [84]. The GUARD study suggests it has potential in preventing cardiac surgery-associated AKI, but it did not significantly improve the incidence of AKI or renal function [85]. The HGF receptor c-met plays a protective role in renal tubular epithelium [86]. The loss of c-met exacerbates kidney injury and increases apoptosis and inflammation. Levels of HGF and soluble cMet are significantly associated with mortality in AKI patients and can serve as prognostic biomarkers, enhancing the predictive value of traditional prognostic indicators [87].

Biomarkers of renal repair and stress response

Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7)

TIMP-2 and IGFBP-7 are associated with G1 cell cycle arrest. By inhibiting cyclin-dependent kinase complexes, they play a role in early cell stress and can be detected in the initial stage of ischemia or toxin-induced AKI (within 24 h), referred to as "renal troponins." The urine concentration of [TIMP-2] [IGFBP-7] is an important biomarker reflecting cellular stress and has been approved by the FDA and EMEA to predict the risk of AKI (Stage II and III) within 12 h in critically ill patients, particularly performing well in patients with cardiac or respiratory failure [3]. NephroCheck®, based on [TIMP-2] [IGFBP-7], enhances the accuracy of identifying high-risk AKI patients [88, 89]. One study found that values of [TIMP-2] ·[IGFBP-7] ≥ 0.3 indicate high risk, and > 2 indicates the highest risk, with sensitivity and specificity of 89% and 95%, respectively [90]. Another prospective study confirmed that this biomarker predicts the risk of renal function not recovering after AKI and, when combined with other indicators, improved prediction accuracy (AUC 0.852) [91]. Additionally, a meta-analysis for cardiac surgery-related AKI showed high predictive value within the first 24 h post-surgery (AUC 0.83) [92]. Although [TIMP-2] [IGFBP-7] has an advantage for early AKI diagnosis, its performance is affected by factors such as sampling time and the severity of AKI, showing some heterogeneity. The KDIGO standards focus on renal function changes rather than the injury itself, which may lead to "false positives" or "false negatives" [3]. Nevertheless, [TIMP-2] [IGFBP-7] has provided important evidence for early assessment and management of AKI in various situations, highlighting the importance of intervention strategies based on this biomarker.

Dickkopf-related protein 3 (DKK3)

DKK3, a member of the Dickkopf family, modulates the Wnt/β-catenin signaling pathway and is involved in cellular differentiation, proliferation, and apoptosis. Urinary DKK3, secreted by renal tubular cells, acts as a profibrotic glycoprotein linked to tubulointerstitial fibrosis phenotypes, enhancing diagnostic accuracy for kidney injury [93]. Studies have demonstrated that preoperative urinary DKK3-to-creatinine ratios above 471 pg/mg can independently predict the risk of postoperative AKI and long-term renal function loss after cardiac surgery, outperforming traditional markers (net reclassification improvement value of 0.32, $p < 0.0001$). Additionally, DKK3 identifies high-risk patients, particularly those not undergoing remote ischemic preconditioning [94]. It also serves as an independent predictor of CI-AKI, with urinary DKK3-to-creatinine ratios significantly elevated (~ 3.8-fold, $p = 0.047$) in affected patients [95]. These findings underscore the clinical relevance of DKK3 in various AKI settings.

Netrin-1

Netrin-1 is a neuroguidance protein that is widely expressed in various tissues, but its expression is relatively low in renal tubular cells. Studies have found that the urinary excretion of netrin-1 is significantly increased in patients with AKI, while no such change is observed in healthy volunteers, suggesting that urinary netrin-1 could be a promising biomarker for early kidney damage [96]. Further research shows that urinary netrin-1 levels are significantly elevated in patients with acute ischemic kidney injury, contrast-induced AKI, sepsis-induced AKI, and drug-induced AKI [97]. Similar findings were observed in studies on septic AKI, where early increases in urinary netrin-1 indicate its potential as an early biomarker for septic AKI [98].

Biomarkers of renal tubular filtration

Cystatin C (CysC)

CysC is a cysteine proteinase inhibitor synthesized by nucleated cells, filtered by the glomerulus, and fully reabsorbed and degraded in the proximal tubules. Since it is unaffected by muscle mass, gender, and age, CysC is more stable in assessing kidney function, particularly in elderly or muscle disease patients. Studies show that urinary CysC levels 0–12 h after cardiac surgery are associated with AKI and may rise earlier than serum creatinine, though the association weakens after adjusting for age and other factors, requiring further validation [99]. Preoperative eGFR calculated with CysC (eGFR-CysC) is significantly associated with postoperative AKI risk, with a significant increase in risk when eGFR-CysC drops below 90, outperforming traditional eGFR-Cr [100]. Furthermore, in total aortic arch replacement(TAAR), serum CysC has shown good predictive capability (AUC-ROC 0.864) [28], supporting early identification of postoperative AKI. However, CysC levels are influenced by factors such as smoking and alcohol consumption, which limits its widespread use.

Proenkephalin (PENK)

PENK is a member of the enkephalin peptide family and is freely filtered in the glomerulus [101]. As a result, PENK can sensitively detect AKI and is associated with poor prognosis in critical illness, sepsis, heart failure, CKD, and kidney transplantation [102, 103]. Studies have shown that PENK demonstrates superior predictive ability over conventional eGFR in septic patients, reliably and sensitively predicting AKI, organ failure, and mortality [101, 104], with plasma PENK levels accurately reflecting glomerular filtration rate. It is particularly applicable to sepsis and heart disease patients. Furthermore, elevated PENK levels are closely associated with poor long-term prognosis in AKI and heart diseases, outperforming traditional creatinine markers. PENK may also reveal the role of endogenous opioids in the regulation of kidney function, expanding its clinical application prospects [105].

Biomarkers of oxidative stress

Superoxide dismutase 1 (SOD1)

SOD1 is an endogenous antioxidant enzyme that catalyzes the conversion of superoxide anions into molecular oxygen and hydrogen peroxide. It is primarily found in renal tubular epithelial cells. Studies have shown that in patients with severe AKI after cardiothoracic surgery, urinary SOD1 concentration (AUC 0.85) and total SOD activity (AUC 0.83) are significantly elevated, indicating that SOD1 has important early predictive value and serves as a crucial marker for intervening in severe AKI [106]. Additionally, red blood cell SOD1 activity is significantly reduced in septic shock patients, with a decrease below 3.32 U/mg Hb associated with an increased risk of AKI (AUC 0.686). Adjusted analyses further suggest that increased SOD1 activity is significantly linked to AKI protection, supporting its potential as an early diagnostic and intervention biomarker for AKI [107].

Other biomarkers

MicroRNAs (miRNAs)

miRNAs are endogenous non-coding RNAs, approximately 19–23 nucleotides in length, that play critical roles in biological processes such as cell proliferation, differentiation, metabolism, and apoptosis. Studies have shown that miRNAs are not only potential biomarkers for AKI but also therapeutic targets [108]. miRNA-210 and miRNA-320 are upregulated in AKI patients, with miRNA-210 serving as a predictor of mortality [109]. Exosomal miRNAs (exomiRs) also hold significant value in the early prediction of CSA-AKI in children. miRNA-21 is upregulated across various AKI types [110, 111], demonstrating its potential as a biomarker, though further experimental research is needed.

BPIFA2 salivary protein

BPI fold-containing family A member 2 (BPIFA2) is a salivary protein primarily expressed in the parotid glands [97]. Studies have shown that it is secreted by ARPCs in LPS-induced AKI, exerting anti-fibrotic effects, helping to restore endothelial function, and inhibiting LPS-induced endothelial-to-mesenchymal transition (EndMT). As an antimicrobial peptide, BPIFA2 may play a crucial role in preventing endothelial cell transition and promoting kidney repair [112]. Additionally, research has found that AKI can induce BPIFA2 expression in the kidneys within 3 h and its levels can be detected in plasma and urine within 6 h. Compared to healthy individuals, BPIFA2 levels are significantly elevated in AKI patients, making it a promising potential biomarker for early AKI [113].

The biomarkers in clinical practice: challenges and strategies

Biomarkers are crucial for diagnosing and predicting AKI, especially for early intervention in high-risk patients. However, their clinical use faces challenges such as validation, standardization, and issues with sensitivity and specificity. Addressing these challenges is key to enhancing their global applicability and clinical impact. Additionally, the limitations of single biomarkers have led to the development of multi-biomarker strategies to improve diagnostic accuracy and patient outcomes.

Validation and standardization challenges

Inconsistent assay methods across laboratories and populations hinder biomarker standardization. For instance, NGAL levels are sensitive to sample handling and storage conditions, remaining stable for up to 36 months at -70 °C but degrading significantly at -20 °C [114], highlighting the need for optimized storage conditions. Additionally, variability in detection thresholds across studies limits diagnostic reliability, reinforcing the need for standardized methods [115]. Not only are detection methods and storage conditions in need of standardization, but high-level strategic frameworks are also essential. According to the consensus from the 31st Acute Disease Quality Initiative (ADQI) meeting (Statement 4), predictive enrichment strategies and biomarkers should be utilized to identify patients with shared pathobiological features. Furthermore, Statement 9 emphasizes that endpoints in Phase 2 clinical trials should reflect biological responses and align with patient outcomes, ensuring both biological plausibility and clinical relevance (Statements 6 and 7) [116]. The clinical application of biomarkers relies heavily on standardized detection methods and reliable cutoffs. Recent studies have validated specific urinary CCL14 thresholds (1.3 and 13 ng/ml) for predicting persistent severe AKI. The low cutoff shows high sensitivity (91%), allowing early risk identification, while the high cutoff achieves high specificity (93%). These findings demonstrate how standardized methods and defined thresholds can optimize AKI biomarker use [65]. Similarly, UHPLC/MS/MS quantification of urinary NGAL showed high sensitivity (90%) and specificity (92.5%) for AKI diagnosis, emphasizing the need for standardized detection methods [117]. Similarly, studies have indicated that pNGAL demonstrates optimal sensitivity and specificity for AKI diagnosis 4–8 h after cardiopulmonary bypass. However, due to study heterogeneity and the lack of assay standardization, its diagnostic efficacy remains inconclusive and requires further validation [118]. Validating such methods across different platforms and institutions not only ensures consistency and reproducibility but also enhances their clinical reliability. These findings underscore the importance of collaborative efforts in developing rigorous validation frameworks for biomarker standardization.

Strategy of combining biomarkers

Single biomarkers show potential for early AKI diagnosis, but their sensitivity and specificity remain limited. For instance, urinary IL-18 demonstrates 92% sensitivity and 100% specificity, but its performance is influenced by comorbidities and AKI etiology [119]. As a result, combining multiple biomarkers has emerged as a key strategy to optimize diagnosis. Recent initiatives, such as the 23rd ADQI consensus, recommend integrating validated biomarkers (e.g., NGAL, TIMP-2×IGFBP7) with damage and functional markers to enhance diagnostic accuracy, sensitivity, and treatment outcomes [120, 121]. For post-cardiac surgery patients, the combination of IL-18 and KIM-1 shows the highest predictive value (AUC 0.93) for identifying high-risk cases suitable for clinical trials [122]. Similarly, a study on CI-AKI found urinary IL-18, KIM-1, and renal resistive index (RRI) to be independent predictors for early diagnosis, with combined assessments improving accuracy [123]. Conversely, others suggest that serum L-FABP and plasma NGAL form the optimal combination for early CI-AKI prediction [124]. In obstructive nephropathy and cisplatin-induced nephrotoxicity studies, combinations like the EGF/MCP-1 ratio, urinary NGAL, and urinary KIM-1 outperform single biomarkers in predicting kidney injury progression, helping prevent adverse long-term outcomes [125–127]. The limitations of single biomarkers have accelerated the adoption of multi-biomarker panels for early AKI diagnosis, with different combinations demonstrating distinct advantages across various pathological contexts (Supplementary Table 1). This approach not only enhances diagnostic sensitivity and specificity but also lays a foundation for personalized risk assessment and targeted interventions, ultimately reducing long-term adverse outcomes and significantly improving patient prognosis.

Conclusions

While the development of biomarkers has shown potential to enhance early diagnosis, prognostic prediction, and risk stratification of AKI, their widespread clinical application is still evolving. These biomarkers may eventually contribute to personalized care and precise clinical decision-making and may inform the development of future therapies. However, their limitations in specificity, predictive accuracy, and clinical applicability remain. Future research should focus on identifying more sensitive and specific biomarkers and validating their clinical value through large-scale trials.

Abbreviations

CT	Computed Tomography
MRI	Magnetic Resonance Imaging
FDA	Food and Drug Administration
NIH	National Institutes of Health
BEST	Biomarkers, EndpointS, and other Tools
EMEA	European Medicines Evaluation Agency
AKI	acute kidney injury
AKD	acute kidney disease
CKD	Chronic Kidney Disease
RIFLE	Risk, Injury, Failure, Loss, and End-stage kidney disease
pRIFLE	pediatric Risk, Injury, Failure, Loss, and End-stage kidney disease
AKIN	Acute Kidney Injury Network
KDIGO	Kidney Disease: Improving Global Outcomes
ICU-AKI	Intensive Care Unit-Acute Kidney Injury
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic
ACS	Acute Coronary Syndromes

AKI-D	Acute Kidney Injury Requiring Dialysis
HRS	Hepatorenal Syndrome
PRA	Prerenal Azotemia
SCr	Serum Creatinine
kinetic eGFR	kinetic Estimated Glomerular Filtration Rate
ATN	Acute Tubular Necrosis
CI-AKI	Contrast-Induced Acute Kidney Injury
VIKI	Vancomycin-Induced Kidney Injury
RRT	Renal Replacement Therapy
NGAL	Neutrophil Gelatinase-Associated Lipocalin
ACSL4	Acyl-CoA Synthetase Long-Chain Family Member 4
KIM-1	Kidney Injury Molecule-1
uKIM-1	urinary Kidney Injury Molecule-1
NAG	N-acetyl-β-D-glucosaminidase
TAAR	Total Aortic Arch Replacement
uNAG	urinary N-acetyl-β-D-glucosaminidase
L-FABP	Liver-Type Fatty Acid-Binding Protein
hL-FABP	Human Liver-type Fatty Acid Binding Protein
SBP1	Selenium Binding Protein 1
GPX4	Glutathione Peroxidase 4
DKK3	Dickkopf-related protein 3
IL-18	Interleukin-18
IL-9	Interleukin-9
AR	Acute Rejection
ILC2s	Type 2 innate lymphoid cells
MCP-1	Monocyte Chemotactic Protein-1
OPN	Osteopontin
CCL14	C-C Motif Chemokine Ligand 14
CXCL9	C-X-C Motif Chemokine Ligand 9
TIMP-2	Tissue Inhibitor of Metalloproteinase-2
IGFBP-7	Insulin-Like Growth Factor-Binding Protein-7
NephroCheck®	[TIMP-2] [IGFBP-7
IGFBP-3	Insulin-Like Growth Factor-Binding Protein-3
CysC	Cystatin C
eGFR CysC	estimated Glomerular Filtration Rate based on Cystatin C
γ-GT	γ-glutamyl transpeptidase
uGGT	urinary γ-glutamyl transferase
HGF	Hepatocyte growth factor
RAS	Renin-Angiotensin System
miRNAs	microRNAs
SuPAR	Soluble Urokinase Plasminogen Activator Receptor
FSGS	Focal Segmental Glomerulosclerosis
CHI3L1	Chitinase-3-Like Protein 1
uCHI3L1	urinary Chitinase-3-Like Protein 1
TNFR	Tumor Necrosis Factor Receptor Type
sTNFR	soluble tumor necrosis factor receptor
FKN	fractalkine
UMOD	Uromodulin
THP	Tamm-Horsfall Protein
AGT	Angiotensinogen
ALP	Alkaline phosphatase
uALP/uCr	Urinary Alkaline Phosphatase to Creatinine
MURs	Molecularly Activated Urine Report Probes
uGGT/uCr	Urinary Gamma-Glutamyl Transferase to Creatinine
uUMOD	urinary Uromodulin
EGF	Epidermal growth factor
DKD	Diabetic Kidney Disease
EGFR	Epidermal growth factor receptor
uEGF	Urinary EGF
MAKE	Major Adverse Kidney Events
SOD1	Superoxide Dismutase 1
BPIFA2	BPI fold-containing family A member 2
ARPCs	Actin-related protein complexes
EndMT	Endothelial-To-Mesenchymal Transition
ADQI	Acute Disease Quality Initiative
ELISA	Enzyme-Linked Immunoadsorption Test
IHC	Immunohistochemistry
TAL Cells	Renal medullary ascending branch thick segment epithelial cells
ADHF	Acute decompensated heart failure
AIN	acute interstitial nephritis

Supplementary Information

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Supplementary Material 1

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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