Annals of Intensive Care 16 (2026) 100017

Contents lists available at ScienceDirect

Annals of Intensive Care

journal homepage: www.elsevier.com/locate/aicoj

Review

What new renal biomarkers tell us about renal physiology☆ Collection: physiology applied to ICU

Melanie Meersch-Dini[a,*], Michael Joannidis[b], Silvia De Rosa[c], Zoltan Endre[d], Marlies Ostermann[e]

[a] Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster, Münster, Germany
[b] Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University of Innsbruck, Innsbruck, Austria
[c] Centre for Medical Sciences - CISMed, University of Trento, Trento, Italy
[d] Department of Nephrology, Prince of Wales Hospital, and School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Sydney, NSW, Australia
[e] Department of Critical Care, King's College London, Guy's and St Thomas' NHS Foundation Hospital, London, United Kingdom

ARTICLE INFO

Keywords:
Physiology
Kidneys
Acute kidney injury
Biomarkers
Molecules
Imaging

ABSTRACT

The kidney plays a vital role in maintaining internal homeostasis through waste elimination, electrolyte and acid-base regulation, and endocrine functions. Recent advances in renal biomarkers have expanded our understanding of kidney physiology by providing detailed insights into the complex mechanisms underlying renal function and injury, beyond traditional measures like serum creatinine and urine output. These novel biomarkers reflect distinct physiological processes, including glomerular filtration, tubular cell stress response, tubular cell damage, inflammation and repair processes within the kidney.

Markers such as cystatin C and proenkephalin serve as more reliable indicators of glomerular filtration rate (GFR), almost unaffected by confounding factors like muscle mass, thus offering more reliable information about renal function than serum creatinine. Biomarkers including Tissue inhibitor of metalloproteinases-2 and insulin like growth factor binding protein 7 (TIMP-2 and IGFBP7) reveal early cellular responses to stress by indicating G1 cell cycle arrest in tubular epithelial cells, a process intended to provide protection against injury. Neutrophil gelatinase-associated lipocalin (NGAL) and related molecules provide information on tubular damage and the kidney's acute damage responses. Chemokines like C-C motif chemokine ligand 14 (CCL14) and CXCL9 highlight the role of immune cells in kidney inflammation and tissue repair, reflecting immune-mediated aspects of renal physiology. In addition to molecular and cellular biomarkers, urine microscopy can provide insightful information about tubular cell health. Further, advanced imaging techniques such as multiparametric magnetic resonance imaging (mpMRI) enable non-invasive evaluation of renal perfusion, oxygenation, and fibrosis. mpMRI provides spatial and functional data that deepen our understanding of renal tissue dynamics and the progression from acute injury to chronic kidney disease (CKD). Together, these biomarkers offer a multidimensional view of kidney physiology, distinguishing between functional changes, cellular stress responses, and structural injury. By illuminating the diverse biological pathways in both healthy and injured kidneys, they enhance our knowledge of renal pathophysiology, indicate underlying mechanisms, enable the identification of specific types of AKI, and provide opportunities to stratify patients for intervention trials.

Abbreviations: AIN, Acute interstitial nephritis; AKI, Acute kidney injury; AP, Alkaline phosphatase; AUC, Area under the curve; CCL14, C-C- motif chemokine ligand 14; CKD, Chronic kidney disease; CXCL9, C-X-C motif ligand 9; GFR, Glomerular filtration rate; GGT, GGT, gamma-glutamyltransferase; GST, Glutathione-S-transferase; IGFBP7, Insulin like growth factor binding protein 7; IL, Interleukin; KIM-1, Kidney injury molecule 1; MRI, Magnetic resonance imaging; NGAL, Neutrophil gelatinase associated lipocalin; PENK, Proenkephalin A; RRI, Renal resistive index; RRT, Renal replacement therapy; RTEC, Renal tubular epithelial cells; TIMP-2, Tissue Inhibitor of Metalloproteinases 2.

* Corresponding author.
E-mail address: meersch@uni-muenster.de (M. Meersch-Dini).

https://dx.doi.org/10.1016/j.aicoj.2025.100017
; Received in revised form 12 December 2025

Background

As principal excretory organs of the human body, the kidneys fulfil critical physiological functions, including the elimination of metabolic waste products, the regulation of electrolyte and acid–base homeostasis, and the modulation of endocrine activities. Owing to its extensive vascularization and high metabolic activity, the kidneys are inherently predisposed to injury, including inflammation, ischemia-reperfusion, nephrotoxicity, and venous congestion. Acute kidney injury (AKI), a clinical syndrome defined by a rapid decline in kidney function after an insult, is a frequent complication of critical illness, affecting more than 50% of patients in the intensive care unit (ICU) [1–4]. An episode of AKI can, even in mild forms, be associated with immune dysfunction, bleeding, delirium, congestive heart failure, chronic kidney disease (CKD) up to end-stage renal disease, impaired quality of life, and reduced survival [5].

Biomarkers (also known as biological markers) are objectively measurable indicators of a biological process, condition, or disease state. In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [6]. Biomarkers can include biological molecules, images, or physiologic measurements. Traditionally, the biomarkers to describe renal function and indicate AKI are serum creatinine and urine output [7]. Whilst used worldwide, they are relatively late markers, not renal specific, confounded by many different conditions and poor indicators of underlying pathophysiology.

This gap has prompted increasing interest in alternative and/or adjunct renal biomarkers, in particular markers that enable earlier and more accurate detection of kidney injury and provide information about underlying biological processes such as tubular stress, inflammation, immune activation and tissue remodelling [8]. This review will focus on the most relevant adjunct renal biomarkers and discuss what they tell us about renal (patho-) physiology.

Diagnosis and limitations of current AKI criteria

Both, serum creatinine and urine output are reliable biomarkers in patients with stable kidney function but perform less well in acute settings where kidney function may decline rapidly or fluctuate. Serum creatinine rise is delayed in following renal injury (often 24−36 h), its half-life increases as GFR declines, and it can be influenced by substances affecting tubular secretion. Urine output is affected by fluid balance, diuretics, and urinary obstruction. Neither marker provides information on AKI etiology, site of injury, underlying mechanisms, or likelihood of recovery. Given these significant limitations, the Acute Dialysis Quality Initiative (ADQI) previously called for incorporation of adjunct biomarkers into the definition of AKI (Fig. 1) [9].

Advancing Renal Diagnostics: Integrating Novel Biomarkers Beyond Serum Creatinine and Urine Output

Biomarkers may take various forms including molecules, specific characteristics in samples (e.g., urine, blood, tissues), imaging, electrocardiographic data, or histopathology (Table 1). They are applied to detect disease processes at an early stage, assess disease progression, evaluate underlying pathophysiology, monitor treatment response, and predict outcomes.

Molecular renal biomarkers

A variety of molecules have been discovered and validated across different patient populations (Fig. 2) [10]. Physiologically, they can be stratified into two main categories. The first category consists of molecules that are freely filtered by the glomerulus (e.g., α1-microglobulin, β2-microglobulin, light chains, cystatin C, proenkephalin), thus reflecting glomerular function. Under normal physiologic conditions, these biomarkers are completely reabsorbed by the proximal tubular cells and only appear in the urine in case of dysfunction. The second group includes molecules of tubular stress and damage which are upregulated in response to stress or damage stimuli and then become detectable in urine and/or blood. These include cell cycle arrest markers like insulin-like growth factor binding protein 7 (IGFBP-7) and tissue inhibitor metalloproteinase 2 (TIMP2), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and liver-type fatty acid binding protein (L-FABP). A third group encompasses biomarkers that are released by inflammatory cells involved in AKI and contribute to kidney injury or repair. For instance, interleukin-18 (IL-18) is secreted by macrophages and neutrophils in the kidneys whereas C-C motif chemokine ligand 14 (CCL14) is mainly produced by macrophages and monocytes and

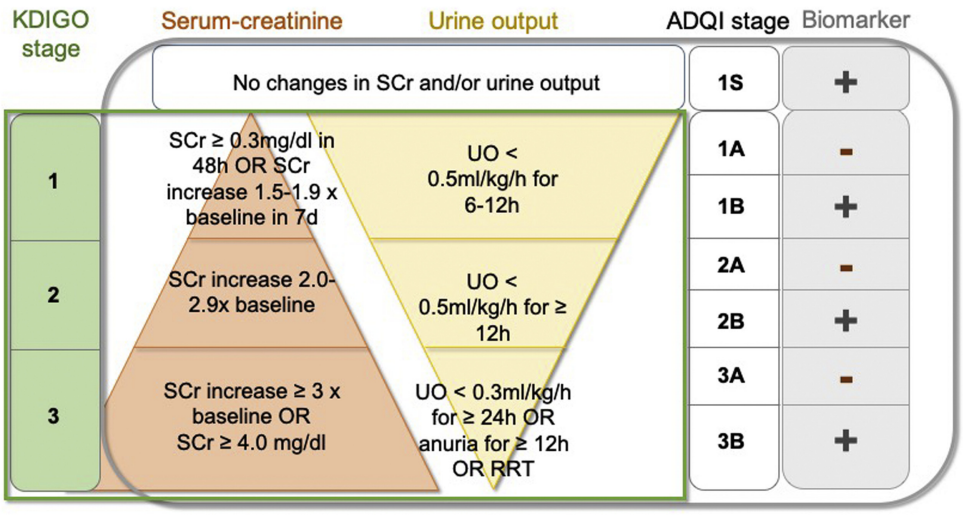

Fig. 1. Diagnosing Criteria of AKI.
Diagnosing criteria as recommended by KDIGO (green line) and by ADQI (grey line). ADQI stage 1s refers to the term "subclinical" AKI.
Abbreviations: ADQI; Acute Dialysis Quality Initiative; KDIGO; Kidney Disease Improving Global Outocmes; SCr, serum creatinine; RRT; renal replacement therapy; UO, urine output

Table 1
Selected biomarkers and their diagnostic potential.

Biomarker	Biological sample	Half life	Time from nephrotoxic trigger to diagnostic concentration	What the marker reveals / measures	Confounding factors
Molecules					
Markers of kidney function					
Cystatin C	Serum or urine	1.5 – 2 h	12 – 24 h	Freely filtered by the glomeruli and almost completely reabsorbed and catabolized by the proximal tubular cells; no tubular resorption or secretion	Elevated in CKD; confounded by age, sex, inflammatory state, diabetes, low albumin, glucocorticoids
Proenkephalin	Serum	Exact half-life not known; stable in blood up to 48 h	Peak level at ~24 h after kidney insult	Freely filtered by the glomeruli; plasma levels correlate strongly with GFR	Elevated in CKD; may be less sensitive than SCr or cystatin C
α1-microglobulin	Urine			Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	
β2-microglobulin	Urine			Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	
Markers of tubular stress / damage					
TIMP-2*IGFBP7	Urine	Exact half life not known	4–5 h	Markers of G1 cell cycle arrest which renal tubular epithelial cells undergo when exposed to stress	Decline in performance if measured beyond 12 h after an AKI event
Markers of tubular damage					
Neutrophil gelatinase associated lipocalin (NGAL)	Serum or urine	10–20 minutes	2–4 h after kidney insult	25 kDa (monomeric) and 45 kDa (homodimeric) undergo glomerular filtration and reabsorption in healthy tubular cells; 25 kDa and 135 kDa (heterodimeric) are released into urine following tubular damage	Confounded by sepsis, UTI, CKD, inflammation
Kidney injury molecule-1 (KIM-1)	Urine	Varies with severity of kidney injury and other factors, including sepsis	12–24 h after kidney insult	Released into urine following ischemic or nephrotoxic tubular damage	Mixed performance in chronic diseases, including immune disorders and cancer
Liver-type fatty acid binding protein (L-FABP)	Urine	~75 h	4–6 h after kidney insult	Freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage	Confounded by anemia in people without diabetes
C-C- motif chemokine ligand 14 (CCL14)	Urine	Not known	Within 36 h of AKI onset	Produced by renal tubular cells in response to injury	Confounded by comorbid conditions, including cancer and inflammation
Markers released by inflammatory cells					
C-X-C ligand 9 (CXCL9)	Urine			CXCL9 is notably produced by renal tubular epithelial cells in response to IFN-γ	
Specific characteristics					
Urine microscopy	RBCs			The presence of RBCs, especially dysmorphic RBCs, suggests glomerular injury, which can be seen in conditions like glomerulonephritis.	Time and operator dependent
	WBCs			The presence of WBCs indicates inflammation or infection within the urinary tract or kidneys, such as in pyelonephritis or interstitial nephritis.	
	RTECs			These cells indicate tubular injury, ATI, the primary pathology of AKI.	
	Casts			Granular Casts: Usually indicative of ATI, but may represent degenerate WBC or RBC Casts Hyaline Casts: Often seen in low perfusion states and are generally non-specific RBC Casts: Suggest glomerulonephritis WBC Casts: Indicate interstitial nephritis or pyelonephritis Epithelial Cell Casts: Reflect tubular damage	
Dipstick proteinuria	Urine			The presence of protein in the urine indicates glomerular damage or increased glomerular permeability, which is a hallmark of kidney disease, especially for CKD	
Imaging techniques					
Doppler ultrasound	Intrarenal venous flow			Alterations in intrarenal venous flow, such as increased renal venous pressure, can lead to impaired renal perfusion and subsequent tubular injury. This hemodynamic disturbance can exacerbate renal ischemia and contribute to the development and progression of AKI.	
	RRI			Elevated RRI values indicate increased vascular resistance which can be due to intrarenal vasoconstriction or interstitial edema	

Abbreviations: AKI, acute kidney injury; ATI, acute tubular injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; IFN-γ, interferon-γ; RBC, red blood cells; RRI, renal resistive index; RTEC, renal tubular epithelial cells; WBC, white blood cells.

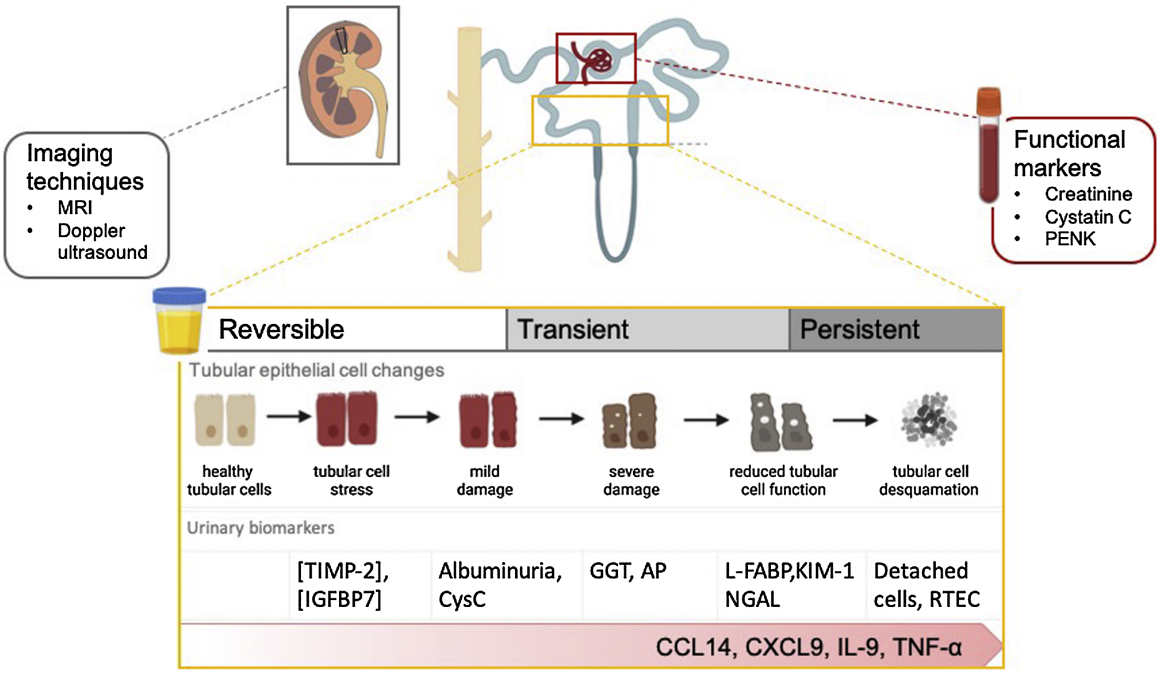

Fig. 2. Biomarker overview including a conceptual model illustrating the temporal dynamics of urinary biomarker release during the progression of AKI.
The sequence begins with healthy renal tubular epithelial cells (RTECs) exposed to cellular stress, advancing through mild and severe structural damage, functional impairment, and eventual epithelial cell desquamation. Inflammatory processes occur concurrently along this continuum. Specific biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL) and C–C motif chemokine ligand 14 (CCL14), are associated with distinct phases of injury.
In addition, functional markers and imaging techniques add information.
Abbreviations: AP, alkaline phosphatase; CCL14, C–C motif chemokine ligand 14; CysC, cystatin C; GGT, gamma-glutamyltransferase; IGFBP7, insulin-like growth factor-binding protein 7; L-FABP, liver-type fatty acid-binding protein; MRI, magnetic resonance imaging; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; RTEC, renal tubular epithelial cell; TIMP-2, tissue inhibitor of metalloproteinases 2.

plays a role in tissue repair and immune cell recruitment to injury sites. All biomarkers are released in response to specific triggers, have unique kinetic profiles and play a role in the development, progression and resolution of AKI.

Biomarkers of glomerular function

Cystatin C

Cystatin C is a small, non-glycosylated protein which is ubiquitously expressed by virtually all nucleated cells. In the kidneys, it is freely filtered by the glomeruli and almost completely reabsorbed and catabolized by the proximal tubular cells via megalin-mediated endocytosis with negligible urinary excretion under normal physiologic conditions. In AKI, impaired glomerular filtration leads to a rapid rise in serum Cystatin C, while proximal tubular dysfunction can increase urinary Cystatin C due to reduced reabsorption [11].

Cystatin C is not affected by muscle metabolism compared to creatinine, though there are other factors such as adiposity, inflammation, corticosteroids use and thyroid function that can influence its levels [12]. In AKI, serum Cystatin C rises earlier than creatinine, providing improved sensitivity and specificity for early detection and severity assessment of AKI across different clinical settings [13]. Some studies demonstrate that serum Cystatin C has a high diagnostic accuracy for AKI prediction, outperforming creatinine in early phases of injury [14,15].

Although urinary cystatin C can indicate tubular injury in specific situations, compared to serum cystatin C, its diagnostic performance remains limited [11,14,16].

Proenkephalin

Proenkephalin A (PENK, aka “proenkephalin A 119-159”) is a relatively stable byproduct of the cleavage of the precursor polypeptide preproenkephalin A along with several active opioid peptides, including Met-enkephalin and Leu-enkephalin [17]. These peptides play important roles in the modulation of pain, stress response, and immune function. Enkephalins primarily act on delta-opioid receptors, which are widely expressed in non-neuronal tissues. Delta opioid receptors are also expressed in renal tissue, and their activation can promote vasodilation and natriuresis, potentially protecting against ischemic or toxic injury by improving perfusion and facilitating excretory function [18].

PENK is freely filtered by the glomeruli and plasma levels correlate strongly with GFR. In AKI, impaired glomerular filtration leads to increased plasma PENK [19,20]. The relationship between PENK and delta-opioid receptor activity suggests that changes in PENK may not only reflect filtration impairment but could also be influenced by altered renal hemodynamic and endogenous opioid signalling during injury and repair [17,18,21].

As a marker of GFR, PENK levels are also associated with adverse outcomes, including deterioration of kidney function and mortality [22,23]. In critically ill patients with dialysis-dependent AKI, lower PENK levels have been associated with successful liberation from renal replacement therapy (RRT), indicating improvement in kidney function [24,25]. These findings require validation in larger studies. Also, further evaluation is needed to determine how this marker behaves under specific condition (e.g., unstable hemodynamic situation).

Stress and damage biomarkers

Tissue inhibitor of metalloproteinases 2 and insulin-like growth factor-binding protein 7 (TIMP-2 and IGFBP7)

Under normal physiologic conditions, renal tubular epithelial cells are largely quiescent residing in the G0 phase with low proliferative activity [26]. Cell cycle progression is tightly regulated by the coordinated actions of cyclins, cyclin dependent kinases and their

inhibitors, with the tumor suppressor p53 serving as a central integrator of stress signals and DNA damage responses [27]. This regulatory network ensures homeostasis and prevents inappropriate proliferation or cell loss.

Tubular insult triggers cell cycle arrest, particularly at the G1 checkpoint, mediated by upregulation of p53 and its downstream effector p21, as well as modulation of cyclins and cyclin dependent kinases [28]. G1 arrest serves as an adaptive mechanism to prevent replication of damaged DNA [29]. However, sustained arrest, particularly at the G2/M phase, can lead to maladaptive repair, cellular senescence and secretion of profibrotic factors, and tubular injury promoting progression of renal injury.

TIMP-2 and IGFBP7 are secreted in response to G1 cell cycle arrest in tubular epithelial cells [30,31]. They act as paracrine alarm signals, halting cell cycle and cell proliferation to allow for DNA repair or adaptation to injury [32,33]. TIMP-2 and IGFBP7 have been approved by the U.S. Food and Drug Administration (FDA) as biomarkers for prediction of AKI and have shown utility to stratify patients for intervention studies [34,35].

Neutrophil Gelatinase associated lipocalin (NGAL)

NGAL is a secretory protein that exists in three isoforms (25 kD, 45 kD, 145 kD). NGAL is predominantly produced by activated neutrophils (45 kD and 145 kD) but the smaller molecule is almost exclusively expressed in renal tubular epithelial cells (25 kD) [36]. In the kidneys, systemic NGAL is freely filtered by the glomerulus, and under normal conditions, it is reabsorbed in the proximal tubule via a megalin-dependent mechanism. In response to kidney damage, NGAL expression in distal tubular cells increases, resulting in a marked elevation of NGAL concentrations in both plasma and urine. The impaired reabsorption in the proximal tubule may further contribute to elevated NGAL levels in the urine. As an indicator of kidney damage, elevated NGAL levels have been associated with worse outcomes, including progression of AKI, need for RRT and increased mortality. These findings underpin its value not only in diagnosing AKI but also in predicting the severity of renal dysfunction and potentially guiding therapeutic interventions. However, since NGAL stems from different sources and also represents an acute phase protein, plasma levels are confounded by systemic inflammation, infection, or other non-renal conditions, especially because the diagnostic performance of the tests highly depends on which molecules are detected by the respective assays [37–40].

Molecules released by inflammatory cells

Chemokines play distinct roles in the pathophysiology of AKI by mediating leukocyte recruitment and modulating responses within the kidney. CCL14 is a chemokine implicated in the recruitment of monocytes and other immune cells to sites of injury [41,42]. This recruitment amplifies the local inflammatory response, thereby promoting ongoing tissue damage and hindering the resolution of AKI. Thus, elevated CCL14 levels are strongly associated with the development of persistent severe AKI, particularly in critically ill and post-cardiac surgery patients [43–46]. Mechanistically, CCL14 is thought to perpetuate renal inflammation by sustaining monocyte/macrophage infiltration, thereby promoting ongoing tubular injury and impeding recovery. High urinary CCL14 concentrations reflect a maladaptive, ongoing inflammatory response, predictive of persistent AKI and adverse outcomes. In addition, CCL14 has also shown value in combination with other markers, for instance the furosemide stress test, in predicting absolute indications for RRT in critically ill patients [47]. Ongoing studies are currently exploring the exact role of CCL14 in AKI management [48].

CXCL9 (C-X-C motif ligand 9) is an interferon-γ inducible chemokine that binds to CXC receptor 3, primarily recruiting T cells to the kidneys. In the context of AKI, especially immune-mediated or drug-induced acute interstitial nephritis (AIN), CXCL9 is upregulated in renal tissue and detectable in urine. Its expression drives T cell infiltration and amplifies tubulointerstitial inflammation, contributing to tissue injury. In urine proteomic analyses of 88 patients (31 with biopsy-confirmed AIN), CXCL9 levels were 7.6-fold higher in those with AIN [49]. Accurately distinguishing drug-induced tubular injury, such as immune checkpoint inhibitor–associated AIN, from prerenal causes like hypovolemia remains a challenge in clinical practice, particularly in cancer patients where this distinction impacts the decision whether to continue or discontinue therapy. Recent studies have demonstrated that measurement of urinary biomarkers, including CXCL9, TNF-α, and IL-9, improves diagnostic accuracy and helps differentiating immune-mediated injury from hemodynamic causes, with CXCL9 providing significant discriminative value beyond standard clinical models. Incorporating these biomarkers into usual clinical evaluation may reduce unnecessary treatment interruptions and facilitate timely management of true nephrotoxic injury.

Molecules located in the brush border of the proximal tubular epithelial cells

Gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP) are brush border enzymes of proximal tubular epithelial cells that are released into the urine following tubular injury and microvilli loss [50]. GGT has been studied as an early AKI marker in ICU settings, though rapid depletion after injury and a brief detection window limit its utility [51].

Early prospective studies in critically ill patients showed elevated urinary levels of GGT, AP, N-acetyl-β-D-glucosaminidase (NAG), as well as alpha- and Glutathione S-transferase (GST), at ICU admission in those who developed AKI [52]. After normalization to urinary creatinine, these biomarkers showed strong predictive value. Subsequently, a composite biomarker (calculated as the product of urinary GGT and AP normalized to urinary creatinine) was evaluated in the EARLYARF trial (n = 528) to guide interventions [51]. The diagnostic utility of GGT in this context proved to be highly dependent on both the interval between renal insult and biomarker measurement, and the patient's pre-admission renal function with higher AUCs in patients with CKD [53].

These studies emphasize that biomarker performance is highly context specific but also dependent on appropriate timing of measurement according to physiological kinetics and baseline kidney function [54]. Brush border enzymes are readily available and cheap but have very limited utility because the temporal profile is brief. Certain biomarkers such as NGAL are influenced by baseline kidney function. Whether serial measurement compared to single values provide additional information is uncertain.

Urinary dipstick

Dipstick urinalysis is a simple available diagnostic tool to detect specific characteristics in the urine. The National Institute for Health and Care Excellence (NICE) in the UK recommends performing urine dipstick testing for blood, protein, leucocytes, nitrites, and glucose in all patients as soon as AKI is suspected. However, the results may be non-specific, indicating several potentially treatable glomerular or tubular pathologies such as glomerulonephritis (hematuria and proteinuria), and acute pyelonephritis (pyuria/leucocyturia and nitrites). As with all biomarkers, the results have to be interpreted within the clinical context. For example, the detection of white blood cells in the urine is a non-specific finding but may suggest the presence of an underlying infection or acute interstitial nephritis. Likewise, dipstick haematuria in patients with an indwelling urinary catheter can arise from various causes, including glomerulonephritis or mechanical trauma. Urine dipstick analysis detects haemoglobin

and can yield positive results even after red blood cell lysis. Additionally, it may identify haemoglobinuria resulting from intravascular haemolysis, as well as myoglobinuria due to muscle breakdown. Thus, a positive dipstick result for haemoglobin in the absence of red blood cells may point to a potential diagnosis of rhabdomyolysis.

In the context of AKI, only few studies have examined the impact on proteinuria [55]. Under physiological conditions, low molecular weight proteins that reach the tubular lumen are reabsorbed by tubular cells. Thus, increased levels of proteinuria after AKI could reflect glomerular damage, residual tubular damage or progressive CKD [56,57].

Urinary particles

Particles, including non-squamous epithelial cells (NSEC), renal tubular epithelial cells (RTEC) and transitional epithelial cells (TEC), are released into the urine following tubular epithelial damage [58–60] and may play a role in the progression to CKD [61]. One observational study among cardiac surgical patients showed that elevated RTEC levels 12 and 24 h after ICU admission highly correlated with the incidence of AKI within the following 7 days (AUC 0.946 (95% CI, 0.906–0.972)) [60]. For early AKI, RTEC levels measured 24 h after ICU admission showed the highest AUC 0.881 (95% CI, 0.830–0.921). In addition, RTEC levels increased with increasing severity of AKI. An elevated number of RTECs is likely indicative of cell death and apoptosis, which may be associated with increased severity of renal injury and a less favourable clinical outcome [62]. RTEC counts were significantly elevated in patients receiving RRT, with a strong correlation observed between RTEC levels and both the persistence and severity of AKI. Preliminary findings suggest that RTEC are indicative of structural tubular injury. More research is needed to evaluate their role in predicting clinical outcomes [54].

Imaging techniques

Doppler ultrasound

Doppler ultrasound enables non-invasive evaluation of renal hemodynamics, offering insight into perfusion abnormalities associated with AKI [63]. The renal resistive index (RRI) as well as the measurement of the intrarenal venous flow are of particular interest [64]. Elevated RRI values indicate increased renal vascular resistance which may be due to intrarenal vasoconstriction or interstitial edema. Higher RRI values are associated with the development and severity of AKI and can differentiate between transient and persistent AKI [64,65]. Abnormalities of the intrarenal venous flow, such as increased renal venous pressure, are important signs as they can contribute to impaired renal perfusion and subsequent tubular injury and AKI progression [66].

A critical limitation of ultrasound imaging remains its high operator dependency, as image quality and diagnostic accuracy are significantly influenced by the operator's skills and expertise [67,68]. To enhance diagnostic capabilities in critical care settings, Color pulsed-wave Doppler ultrasound (CPWD-US) has emerged as a pivotal tool in ICUs [69,70]. Its bedside accessibility allows for rapid, non-invasive assessments, making it a promising marker for characterizing AKI.

Magnetic resonance techniques (MRI)

The use of MRI techniques to assess renal dysfunction has expanded in recent years, with multiparametric (mp)MRI offering insights into renal blood flow, oxygenation, and fibrosis without exposure to ionizing radiation. By identifying and quantifying key mechanisms of kidney injury and maladaptive repair—such as capillary rarefication, inflammation, and fibrosis—mpMRI offers potential to enhance our understanding of AKI sub-phenotypes and the transition from AKI to CKD [53,71–73]. Notably, MRI allows reliable assessment of the renal medulla, a region increasingly recognized for its role in AKI pathogenesis [74].

In separate cohorts of critically ill patients with sepsis and COVID-19–associated AKI, significantly reduced renal blood flow (measured by phase-contrast MRI) and cortical perfusion (measured by arterial spin labeling) were observed, in comparison to similar patients without AKI and to healthy controls [75,76]. Similarly, reduced cortical perfusion has been reported in acute presentations of glomerulonephritis and interstitial nephritis [77]. Multiparametric MRI of the kidneys has the potential to address the limitations of existing biomarkers and diagnostic methods to provide a noninvasive, noncontrast, and radiation-free method to assess whole kidney structure and function, and potentially replacing a renal biopsy [78]. However, its clinical applicability remains limited as it is resource-intensive, not yet widely available in acute settings, and evidence from large interventional trials is lacking.

Biomarkers to Improve Diagnostic Precision and Therapeutic Decision-Making in AKI

As these biomarkers reflect distinct physiological and pathophysiological processes, they may enhance diagnostic precision, support the differentiation of different AKI phenotypes, and potentially inform targeted personalised therapeutic decisions, particularly when used in combination. Ongoing studies aim to validate these approaches and explore their clinical utility (Table 2).

Differentiation of pathophysiological processes

The combined use of functional and structural biomarkers, for instance NGAL and PENK, offers insight into the anatomical origin of injury. While elevated NGAL levels are associated with tubular toxicity, alterations in PENK suggest glomerular dysfunction, enabling a differentiation between distinct pathophysiological processes and identification of AKI sub-phenotypes [21,79].

A subset of patients with AKI may exhibit elevated urinary TNF-α, IL-9 and CXCL9, which have been associated with tubulointerstitial nephritis rather than acute tubular necrosis [80]. Data from Moledina et al. suggest that these markers not only refine diagnostic specificity but also identify patients who may benefit from corticosteroid therapy [81]. However, larger validation studies are needed.

In patients with congestive heart failure, serum creatinine may rise during diuretic therapy due to functional volume shifts [82]. Measurement of NGAL can help to distinguish between these benign functional changes and true tubular injury. A normal NGAL level in the setting of rising creatinine suggests functional AKI which may support a decision to continue diuretic therapy and decongestion. In contrast, elevated NGAL concentrations in this setting imply structural damage, warranting a reassessment of therapy and consideration of discontinuation of nephrotoxic agents.

Prognostication of short- and long-term renal outcomes

For predicting the development of CKD, creatinine levels at ICU discharge have proven unreliable, whereas biomarkers have demonstrated superior performance [83]. Also, the trajectory pattern of AKI biomarkers have shown to be associated with the development of major adverse kidney events [84]. For instance, elevated levels of urinary CCL14 are predictive of persistent kidney dysfunction [46,47]. Future research needs to explore their role in determining the optimal time for initiation of RRT in individual patients.

Table 2
Examples of studies that include biomarkers as enrichment or stratification tools.

Trial number	Study title	Included biomarker
NCT05275218	Effect of an Intervention to Prevent Acute Kidney Injury Versus Standard Care in High-risk Patients After Major Surgery (PrevProgAKI)	CCL-14
NCT04647396	Biomarker-guided Intervention to Prevent Acute Kidney Injury (BigpAK-2) [93]	TIMP-2*IGFBP7
NCT06834633	Nephroprotection in Severe Trauma Patients With Kidney Stress (NephroTrauma)	TIMP-2*IGFBP7
NCT06464666	Association Between Renal Resistive Index(RRI) and AKI (Acute Kidney Injury) in Cardiac Surgery Patients With Cardiopulmonary Bypass (CPB)	RRI
NCT06954129	A Pragmatic Clinical Trial Comparing the Risk of Acute Kidney Injury During Treatment With Vancomycin and Piperacillin-Tazobactam vs. Vancomycin and Cefepime in Hospitalized Patients (MONACO)	Cystatin C
NCT06917053	Renal Perfusion and the Development of AKI Following Traumatic Injury (PERTAKI)	Ultrasound
NCT06234592	The Effect of Vasopressor Therapy on Renal Perfusion in Septic Shock (REPERFUSE)	Ultrasound

Beyond molecular biomarkers, mpMRI has shown promise in distinguishing reversible injury from progressive fibrosis following AKI. Studies demonstrate that mpMRI can non-invasively assess renal tissue characteristics such as perfusion, edema, and fibrosis, offering insights into long-term outcomes post-injury [78,85].

Biomarkers for managing drug therapy

In preclinical models, biomarkers have been approved to diagnose drug-induced injury [86]. They facilitate our mechanistic understanding of nephrotoxicity and support the development of safer pharmacologic compounds. In January 2025, the U.S. FDA accepted a Qualification Plan for a urine biomarker panel for the early detection and monitoring of drug-induced AKI in clinical trials, avoiding more invasive tests or inappropriate clinical decision making. For instance, creatinine elevations observed during cimetidine therapy may result from inhibition of the organic anion transport system, rather than true renal injury [87,88]. In such cases, the absence of tubular damage biomarkers can help distinguishing 'pseudo-AKI' from pathological AKI.

Biomarker-Guided Antibiotic Stewardship

As predictors of AKI, it is possible that biomarkers such as NGAL and [TIMP-2]*[IGFBP7] have potential in the context of antibiotic stewardship, particularly in patients receiving nephrotoxic agents like vancomycin or gentamicin [89]. However, further investigation is required and more robust data is needed to give clear recommendations for clinical practice.

Conclusions

Emerging renal biomarkers have transformed our understanding of kidney physiology by providing nuanced insights into the intricate processes governing renal function, injury, and repair. Moving beyond the limitations of traditional markers like serum creatinine and urine output, traditional and new biomarkers capture specific aspects of glomerular filtration, tubular cell stress, and immune-mediated inflammation. Molecular biomarkers coupled with advanced imaging techniques such as multiparametric MRI, offer a comprehensive, dynamic view of renal health and disease progression. The validation of new biomarkers is complex and involves rigorous testing in independent sample cohorts to ensure statistical significance and clinical relevance, and demonstrating both, analytical and clinical validity within the biomarker's intended use. The integration of existing and upcoming tools into clinical practice holds promise for earlier diagnosis, identification of AKI sub-phenotypes, more precise risk stratification, improved trial design and personalized therapeutic strategies to prevent and manage AKI [90–92].

CRediT authorship contribution statement

MM is the guarantor of the content of the manuscript. MM wrote the first draft. MJ, SDR, ZE, MO reviewed all drafts and made edits. The final draft was approved by all authors.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Funding

MM is supported by the German Research Foundation (ME5413/1-2 to MM).

Availability of data and material

Not applicable.

Declaration of competing interest

MM has received lecture fees from Fresenius Medical Care, Baxter, as well as an unrestricted research grant from Baxter. MJ has received honoraria and/or research support from Baxter Healthcare Corp, AM-Pharma, CLS Behring, Fresenius, Biomerieux and Novartis. SDR has received lecture fees from Fresenius Medical Care, Baxter, Estor, Toray, Vantive. ZE has received in-kind biomarker measurement support from Biomerieux and Sphingotec. MO has received research funding from Biomerieux and Baxter (paid to institution).

References

[1] Joannidis M, Meersch-Dini M, Forni LG. Acute kidney injury. Intensive Care Med. 2023;49(6):665–8.
[2] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23.
[3] Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, et al. Sepsis-associated Acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2023;19(6):401–17.
[4] Zarbock A, Weiss R, Albert F, Rutledge K, Kellum JA, Bellomo R, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study. Intensive Care Med. 2023;49(12):1441–55.
[5] Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394 (10212):1949–64.
[6] Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69 (3):89–95.

[7] Ostermann M, Lumlertgul N, Jeong R, See E, Joannidis M, James M. Acute kidney injury. Lancet. 2025;405(10474):241–56.
[8] Meersch M, Mayerhofer T, Joannidis M. Acute kidney injury subphenotyping and personalized medicine. Curr Opin Crit Care. 2024;30(6):555–62.
[9] Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open. 2020;3(10):e2019209.
[10] Ostermann M, Legrand M, Meersch M, Srisawat N, Zarbock A, Kellum JA. Biomarkers in acute kidney injury. Ann Intensive Care. 2024;14(1):145.
[11] Jensen D, Kierulf-Lassen C, Kristensen MLV, Norregaard R, Weyer K, Nielsen R, et al. Megalin dependent urinary cystatin C excretion in ischemic kidney injury in rats. PloS One. 2017;12(6):e0178796.
[12] Chen DC, Potok OA, Rifkin D, Estrella MM. Advantages, limitations, and clinical considerations in using cystatin C to estimate GFR. Kidney360. 2022;3(10):1807–14.
[13] Hooper L, Heung M, Kenes M, Stringer KA, Mueller BA, Pai MP. The kinetics of cystatin C and serum creatinine in AKI. Clin J Am Soc Nephrol. 2025;20(4):477–84.
[14] Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 2011;58(3):356–65.
[15] Soto K, Coelho S, Rodrigues B, Martins H, Frade F, Lopes S, et al. Cystatin C as a marker of acute kidney injury in the emergency department. Clin J Am Soc Nephrol. 2010;5(10):1745–54.
[16] Bagshaw SM, Bellomo R. Cystatin C in acute kidney injury. Curr Opin Crit Care. 2010;16(6):533–9.
[17] Beunders R, Struck J, Wu AHB, Zarbock A, Di Somma S, Mehta RL, et al. Proenkephalin (PENK) as a novel biomarker for kidney function. J Appl Lab Med. 2017;2(3):400–12.
[18] Lin LC, Chuan MH, Liu JH, Liao HW, Ng LL, Magnusson M, et al. Proenkephalin as a biomarker correlates with acute kidney injury: a systematic review with meta-analysis and trial sequential analysis. Crit Care. 2023;27(1):481.
[19] Beunders R, Donato LJ, van Groenendael R, Arlt B, Carvalho-Wodarz C, Schulte J, et al. Assessing GFR with proenkephalin. Kidney Int Rep. 2023;8(11):2345–55.
[20] Hartman SJF, Zwiers AJM, van de Water NEC, van Rosmalen J, et al. Proenkephalin as a new biomarker for pediatric acute kidney injury - reference values and performance in children under one year of age. Clin Chem Lab Med. 2020;58(11):1911–9.
[21] Khorashadi M, Beunders R, Pickkers P, Legrand M. Proenkephalin: a new biomarker for glomerular filtration rate and acute kidney injury. Nephron. 2020;144(12):655–61.
[22] Fuchs MAA, Schrankl J, Wagner C, Daniel C, Kurtz A, Broeker KA. Localization and characterization of proenkephalin-A as A potential biomarker for kidney disease in murine and human kidneys. Biomarkers. 2023;28(1):76–86.
[23] Doukas P, Hartmann O, Arlt B, Jacobs MJ, Greiner A, Frese JP, et al. The role of Proenkephalin A 119-159 in the detection of acute kidney injury after open thoracoabdominal aortic repair. Vasa. 2024;53(1):61–7.
[24] von Groote T, Albert F, Meersch M, Koch R, Porschen C, Hartmann O, et al. Proenkephalin A 119-159 predicts early and successful liberation from renal replacement therapy in critically ill patients with acute kidney injury: a post hoc analysis of the ELAIN trial. Crit Care. 2022;26(1):333.
[25] von Groote T, Albert F, Meersch M, Koch R, Gerss J, Arlt B, et al. Evaluation of Proenkephalin A 119-159 for liberation from renal replacement therapy: an external, multicenter pilot study in critically ill patients with acute kidney injury. Crit care. 2023;27(1):276.
[26] Thomasova D, Anders HJ. Cell cycle control in the kidney. Nephrol Dial Transplant. 2015;30(10):1622–30.
[27] Overstreet JM, Gifford CC, Tang J, Higgins PJ, Samarakoon R. Emerging role of tumor suppressor p53 in acute and chronic kidney diseases. Cell Mol Life Sci. 2022;79(9):474.
[28] Moonen L, D'Haese PC, Vervaet BA. Epithelial cell cycle behaviour in the injured kidney. Int J Mol Sci. 2018;19(7).
[29] He L, Wei Q, Liu J, Yi M, Liu Y, Liu H, et al. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int. 2017;92(5):1071–83.
[30] Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17(1):R25.
[31] Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PloS One. 2014;9(3):e93460.
[32] Wang WG, Sun WX, Gao BS, Lian X, Zhou HL. Cell cycle arrest as a therapeutic target of acute kidney injury. Curr Protein Pept Sci. 2017;18(12):1224–31.
[33] Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. Nephrol Dial Transplant. 2016;31(1):16–22.
[34] Huang F, Zeng Y, Lv L, Chen Y, Yan Y, Luo L, et al. Predictive value of urinary cell cycle arrest biomarkers for all cause-acute kidney injury: a meta-analysis. Sci Rep. 2023;13(1):6037.
[35] See CY, Pan HC, Chen JY, Wu CY, Liao HW, Huang YT, et al. Improvement of composite kidney outcomes by AKI care bundles: a systematic review and meta-analysis. Crit Care. 2023;27(1):390.
[36] Cai L, Rubin J, Han W, Venge P, Xu S. The origin of multiple molecular forms in urine of HNL/NGAL. Clin J Am Soc Nephrol. 2010;5(12):2229–35.
[37] Dai X, Zeng Z, Fu C, Zhang S, Cai Y, Chen Z. Diagnostic value of neutrophil gelatinase-associated lipocalin, cystatin C, and soluble triggering receptor expressed on myeloid cells-1 in critically ill patients with sepsis-associated acute kidney injury. Crit Care. 2015;19(1):223.
[38] Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, et al. Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: a prospective cohort study of patients with sepsis. BMC Nephrol. 2015;16:18.
[39] Glassford NJ, Schneider AG, Xu S, Eastwood GM, Young H, Peck L, et al. The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. Intensive Care Med. 2013;39(10):1714–24.
[40] Bellomo R, See EJ. Novel renal biomarkers of acute kidney injury and their implications. Intern Med J. 2021;51(3):316–8.
[41] Anders HJ, Vielhauer V, Schlondorff D. Chemokines and chemokine receptors are involved in the resolution or progression of renal disease. Kidney Int. 2003;63(2):401–15.
[42] Chung AC, Lan HY. Chemokines in renal injury. J Am Soc Nephrol. 2011;22(5):802–9.
[43] Massoth C, Kullmar M, Enders D, Kellum JA, Forni LG, Meersch M, et al. Comparison of C-C motif chemokine ligand 14 with other biomarkers for adverse kidney events after cardiac surgery. J Thoracic Cardiovasc Surg. 2021.
[44] Bagshaw SM, Al-Khafaji A, Artigas A, Davison D, Haase M, Lissauer M, et al. External validation of urinary C-C motif chemokine ligand 14 (CCL14) for prediction of persistent acute kidney injury. Crit Care. 2021;25(1):185.
[45] Chen YT, Pan HC, Hsu CK, Sun CY, Chen CY, Chen YH, et al. Performance of urinary C-C motif chemokine ligand 14 for the prediction of persistent acute kidney injury: a systematic review and meta-analysis. Crit Care. 2023;27(1):318.
[46] Hoste E, Bihorac A, Al-Khafaji A, Ortega LM, Ostermann M, Haase M, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Med. 2020;46(5):943–53.
[47] Meersch M, Weiss R, Gerss J, Albert F, Gruber J, Kellum JA, et al. Predicting the development of renal replacement therapy indications by combining the furosemide stress test and chemokine (C-C Motif) ligand 14 in a cohort of postsurgical patients. Crit Care Med. 2023;51(8):1033–42.
[48] Sadjadi M, Strauss C, von Groote T, Booke H, Schone LM, Sauermann L, et al. Effects of an extended therapeutic strategy versus standard-of-care therapy on persistent acute kidney injury in high-risk patients after major surgery: study protocol for the randomised controlled single-centre PrevProgAKI trial. BMJ Open. 2025;15(5):e097333.
[49] Moledina DG, Obeid W, Smith RN, Rosales I, Sise ME, Moeckel G, et al. Identification and validation of urinary CXCL9 as a biomarker for diagnosis of acute interstitial nephritis. J Clin Invest. 2024;134(6).
[50] de Geus HR, Betjes MG, Bakker J. Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. Clin Kidney J. 2012;5(2):102–8.
[51] Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int. 2011;79(10):1119–30.
[52] Westhuyzen J, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant. 2003;18(3):543–51.
[53] Sato Y, Yanagita M. Immune cells and inflammation in AKI to CKD progression. Am J Physiol Renal Physiol. 2018;315(6):F1501–12.
[54] Ostermann M, Darmon M, Joannidis M. Renal tubular epithelial cells: a revived kidney biomarker? Intensive Care Med. 2025;51(7):1348–50.
[55] Hsu CY, Hsu RK, Liu KD, Yang J, Anderson A, Chen J, et al. Impact of AKI on urinary protein excretion: analysis of two prospective cohorts. J Am Soc Nephrol. 2019;30(7):1271–81.
[56] Russo LM, Sandoval RM, McKee M, Osicka TM, Collins AB, Brown D, et al. The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: retrieval is disrupted in nephrotic states. Kidney Int. 2007;71(6):504–13.
[57] Parr SK, Matheny ME, Abdel-Kader K, Greevy RA Jr, Bian A, Fly J, et al. Acute kidney injury is a risk factor for subsequent proteinuria. Kidney Int. 2018;93(2):460–9.
[58] Perazella MA. The urine sediment as a biomarker of kidney disease. Am J Kidney Dis. 2015;66(5):748–55.
[59] Perazella MA, Coca SG. Traditional urinary biomarkers in the assessment of hospital-acquired AKI. Clin J Am Soc Nephrol. 2012;7(1):167–74.
[60] Oyaert M, Delanghe J, Brouwers A, Bove T, Schaubroeck H, Delrue C, et al. Renal tubular epithelial cells as an easily accessible biomarker for diagnosing AKI post cardiac surgery. Intensive Care Med. 2025.
[61] Chen J, Zhang H, Yi X, Dou Q, Yang X, He Y, et al. Cellular senescence of renal tubular epithelial cells in acute kidney injury. Cell Death Discov. 2024;10(1):62.
[62] Li ZL, Li XY, Zhou Y, Wang B, Lv LL, Liu BC. Renal tubular epithelial cells response to injury in acute kidney injury. EBioMedicine. 2024;107105294.
[63] Le Dorze M, Bougle A, Deruddre S, Duranteau J. Renal Doppler ultrasound: a new tool to assess renal perfusion in critical illness. Shock. 2012;37(4):360–5.
[64] Cruz EG, Broca Garcia BE, Sandoval DM, Gopar-Nieto R, Gonzalez Ruiz FJ, Gallardo LD, et al. Renal resistive index as a predictor of acute kidney injury and mortality in COVID-19 critically ill patients. Blood Purif. 2022;51(4):309–16.
[65] Haitsma Mulier JLG, Rozemeijer S, Rottgering JG, Spoelstra-de Man AME, Elbers PWG, Tuinman PR, et al. Renal resistive index as an early predictor and discriminator of acute kidney injury in critically ill patients; A prospective observational cohort study. PloS One. 2018;13(6):e0197967.
[66] Kopitko C, Gondos T, Fulop T, Medve L. Reinterpreting renal hemodynamics: the importance of venous congestion and effective organ perfusion in acute kidney injury. Am J Med Sci. 2020;359(4):193–205.

[67] Darmon M, Bourmaud A, Reynaud M, Rouleau S, Meziani F, Boivin A, et al. Performance of Doppler-based resistive index and semi-quantitative renal perfusion in predicting persistent AKI: results of a prospective multicenter study. Intensive Care Med. 2018;44(11):1904–13.
[68] Saade A, Bourmaud A, Schnell D, Darmon M, Group RDS. Performance of Doppler-based resistive index and semiquantitative renal perfusion in predicting persistent acute kidney injury according to operator experience: post hoc analysis of a prospective multicenter study. Crit Care Med. 2022;50(4):e361–9.
[69] Capotondo L, Nicolai GA, Garosi G. The role of color Doppler in acute kidney injury. Arch Ital Urol Androl. 2010;82(4):275–9.
[70] Hansen KL, Nielsen MB, Ewertsen C. Ultrasonography of the kidney: a pictorial review. Diagnostics (Basel). 2015;6(1).
[71] de Caestecker M, Humphreys BD, Liu KD, Fissell WH, Cerda J, Nolin TD, et al. Bridging Translation by Improving Preclinical Study Design in AKI. J Am Soc Nephrol. 2015;26(12):2905–16.
[72] Ralto KM, Rhee EP, Parikh SM. NAD(+) homeostasis in renal health and disease. Nat Rev Nephrol. 2020;16(2):99–111.
[73] Yu SM, Bonventre JV. Acute kidney injury and maladaptive tubular repair leading to renal fibrosis. Curr Opin Nephrol Hypertens. 2020;29(3):310–8.
[74] Tewes S, Gueler F, Chen R, Gutberlet M, Jang MS, Meier M, et al. Functional MRI for characterization of renal perfusion impairment and edema formation due to acute kidney injury in different mouse strains. PloS One. 2017;12(3):e0173248.
[75] Prowle JR, Molan MP, Hornsey E, Bellomo R. Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: a pilot investigation. Crit Care Med. 2012;40(6):1768–76.
[76] Luther T, Eckerbom P, Cox E, Lipcsey M, Bulow S, Hultstrom M, et al. Decreased renal perfusion during acute kidney injury in critical COVID-19 assessed by magnetic resonance imaging: a prospective case control study. Crit Care. 2022;26(1):262.
[77] Dong J, Yang L, Su T, Yang X, Chen B, Zhang J, et al. Quantitative assessment of acute kidney injury by noninvasive arterial spin labeling perfusion MRI: a pilot study. Sci China Life Sci. 2013;56(8):745–50.
[78] Francis ST, Selby NM, Taal MW. Magnetic resonance imaging to evaluate kidney structure, function, and pathology: moving toward clinical application. Am J Kidney Dis. 2023;82(4):491–504.
[79] Romejko K, Markowska M, Niemczyk S. The review of current knowledge on neutrophil gelatinase-associated lipocalin (NGAL). Int J Mol Sci. 2023;24(13).
[80] Moledina DG, Wilson FP, Pober JS, Perazella MA, Singh N, Luciano RL, et al. Urine TNF-alpha and IL-9 for clinical diagnosis of acute interstitial nephritis. JCI Insight. 2019;4(10).
[81] Moledina DG, Wilson FP, Kukova L, Obeid W, Luciano R, Kuperman M, et al. Urine interleukin-9 and tumor necrosis factor-alpha for prognosis of human acute interstitial nephritis. Nephrol Dial Transplant. 2021;36(10):1851–8.
[82] Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137(19):2016–28.
[83] Ravn B, Prowle JR, Martensson J, Martling CR, Bell M. Superiority of serum cystatin C over creatinine in prediction of long-term prognosis at discharge From ICU. Crit Care Med. 2017;45(9):e932–40.
[84] Horie R, Hayase N, Asada T, Yamamoto M, Matsubara T, Doi K. Trajectory pattern of serially measured acute kidney injury biomarkers in critically ill patients: a prospective observational study. Ann Intensive Care. 2024;14(1):84.
[85] Buchanan CE, Mahmoud H, Cox EF, Prestwich BL, Noble RA, Selby NM, et al. Multiparametric renal magnetic resonance imaging for prediction and annual monitoring of the progression of chronic kidney disease over two years. J Clin Med. 2023;12(23).
[86] Kane-Gill SL, Smithburger PL, Kashani K, Kellum JA, Frazee E. Clinical relevance and predictive value of damage biomarkers of drug-induced kidney injury. Drug Saf. 2017;40(11):1049–74.
[87] Nakada T, Kudo T, Ito K. Quantitative consideration of clinical increases in serum creatinine caused by renal transporter inhibition. Drug Metab Dispos. 2023;51(9):1114–26.
[88] Sansoe G, Ferrari A, Castellana CN, Bonardi L, Villa E, Manenti F. Cimetidine administration and tubular creatinine secretion in patients with compensated cirrhosis. Clin Sci. 2002;102(1):91–8.
[89] Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, et al. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. Crit Care Med. 2018;46(3):375–83.
[90] Zarbock A, Forni LG, Ostermann M, Ronco C, Bagshaw SM, Mehta RL, et al. Designing acute kidney injury clinical trials. Nat Rev Nephrol. 2024;20(2):137–46.
[91] Zarbock A, Forni LG, Koyner JL, Bell S, Reis T, Meersch M, et al. Recommendations for clinical trial design in acute kidney injury from the 31st acute disease quality initiative consensus conference. A consensus statement. Intensive Care Med. 2024;50(9):1426–37.
[92] Gordon AC, Alipanah-Lechner N, Bos LD, Dianti J, Diaz JV, Finfer S, et al. From ICU Syndromes to ICU Subphenotypes: Consensus Report and Recommendations for Developing Precision Medicine in the ICU. Am J Respir Crit Care Med. 2024;210(2):155–66.
[93] Zarbock A, Ostermann M, Forni L, Bode C, Wild L, Putensen C, et al. A preventive care strategy to reduce moderate or severe acute kidney injury after major surgery (BigpAK-2); a multinational, randomised clinical trial. Lancet. 2025.