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Open Access Journal of Urology & Nephrology
ISSN: 2578-4676

Emerging Urinary Biomarkers for Early Recognition of Progressive Kidney Injury: Mini Review

Smith P*

Assistant Professor, Department of Urology, Faculty of Medicine, Dalhousie University, Canada

***Corresponding author:** Peter Smith, Assistant Professor, Department of Urology, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Mini Review
Volume 10 Issue 2
Received Date: April 05, 2025
Published Date: April 30, 2025

Abstract

Progressive kidney injury is frequently recognized only after measurable deterioration in glomerular filtration or urine output has occurred. Serum creatinine and urine output remain indispensable clinical measures, but both can lag behind structural or cellular injury. Urinary biomarkers offer an attractive complementary approach because urine directly reflects processes occurring along the nephron and can be collected repeatedly with relatively little invasiveness. This mini review summarizes emerging urinary biomarkers that may support earlier recognition and risk stratification of progressive kidney injury, with emphasis on neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), interleukin-18 (IL-18), tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), C-C motif chemokine ligand 14 (CCL14), urinary cystatin C, and newer molecular approaches including extracellular vesicles and microRNAs. The biological rationale, potential clinical applications, limitations, and future directions of these markers are considered. Current evidence indicates that no single urinary biomarker reliably captures every phenotype of kidney injury. Instead, biomarker panels that integrate tubular injury, cellular stress, inflammation, functional impairment, and recovery signals may provide a more informative picture of disease evolution. Translation into routine practice will require harmonized assays, validated thresholds, population-specific studies, longitudinal evaluation, and evidence that biomarker-guided action improves patient outcomes rather than merely predicting them.

Keywords: Biomarkers; Acute Kidney Injury; Progressive Kidney Injury; NGAL; KIM-1; TIMP-2; IGFBP7; Tubular Injury; Kidney Disease; Early Detection

Introduction

Kidney injury is a dynamic biological process rather than a single laboratory event. Ischemia, sepsis, nephrotoxic exposure, obstruction, inflammation, hemodynamic instability, and metabolic disease can initiate cellular stress that precedes an observable decline in filtration. In clinical practice, serum creatinine and urine output remain the principal functional indicators used to identify acute kidney injury (AKI), but their interpretation can be delayed by changes in creatinine production, volume distribution, baseline kidney function, fluid balance, and timing of injury. This creates an important diagnostic interval during which structural injury may already be evolving while conventional functional measures remain apparently stable [1].

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The search for biomarkers that identify kidney injury earlier has therefore expanded substantially. Urinary biomarkers are particularly attractive because they may arise directly from injured tubular cells, inflammatory pathways, cellular stress responses, or altered tubular handling of proteins. Several markers can increase hours before a conventional creatinine-defined AKI episode becomes apparent. Contemporary evidence increasingly supports viewing biomarkers not simply as replacements for creatinine, but as complementary measurements that describe different dimensions of kidney pathobiology [2].

The clinical need is especially relevant to progressive kidney injury. Patients may move from an initial insult to persistent or worsening dysfunction, renal replacement therapy, incomplete recovery, or chronic kidney disease. Early recognition could allow clinicians to remove nephrotoxins, optimize hemodynamics, adjust medication dosing, intensify monitoring, and identify patients suitable for targeted interventions. The 2026 KDIGO public-review draft also emphasizes the continuum of AKI and acute kidney disease and gives greater attention to structural biomarkers and early risk prediction. However, the guideline notes that no single biomarker performs adequately across all settings and that biomarkers should be interpreted with clinical assessment.

This mini review discusses the principal emerging urinary biomarkers for early recognition of progressive kidney injury, their biological foundations, evidence base, practical limitations, and potential role in future biomarker-guided nephrology [3].

Why Conventional Kidney Function Markers Can Miss Early Injury

Serum creatinine is a marker of filtration rather than direct structural injury. A clinically meaningful rise may require substantial loss of filtration and can be influenced by muscle mass, age, diet, fluid status, medications, and timing. Urine output is valuable and rapidly available, but oliguria is not specific for intrinsic renal injury and may be affected by hemodynamics, diuretics, obstruction, and fluid administration.

These limitations are important because cellular injury can begin before filtration falls. Tubular epithelial cells respond to ischemia and toxins through oxidative stress, mitochondrial dysfunction, cytoskeletal disruption, inflammatory signaling, and cell-cycle arrest. Biomarkers released during these processes may therefore become measurable before a creatinine-defined change. This concept has led to the distinction between functional biomarkers and damage or stress biomarkers [4].

The practical implication is not that creatinine should be abandoned. Rather, a combined framework may be more informative: functional markers establish the degree of filtration impairment, while urinary biomarkers can provide earlier evidence of structural damage or cellular stress. This distinction is particularly relevant when clinicians must decide whether a patient with apparently preserved filtration is nevertheless entering a high-risk trajectory.

Mini Review: Emerging Urinary Biomarkers

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is one of the most extensively studied urinary biomarkers of tubular injury. It is produced by neutrophils and several epithelial tissues, while injured renal tubular epithelial cells can markedly increase NGAL expression. Urinary NGAL may ris e rapidly following ischemic or toxic tubular injury, making it attractive for early AKI recognition [5].

Clinical studies have evaluated NGAL in critical illness, cardiac surgery, transplantation, sepsis, and pediatric populations. Recent evidence suggests variable but generally useful diagnostic performance, with differences attributable to timing, assay platforms, clinical setting, and the definition of AKI. NGAL may also contribute to prediction of progression and need for kidney replacement therapy in selected populations.

A major limitation is biological specificity. Systemic inflammation, infection, chronic kidney disease, and some extra-renal conditions can influence NGAL concentrations. Consequently, an elevated result should not automatically be interpreted as proof of intrinsic renal injury. Urinary NGAL may be most useful when interpreted with the clinical context and a functional marker [6].

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a transmembrane protein that is strongly induced in injured proximal tubular epithelial cells. Its extracellular domain can be released into urine, making urinary KIM-1 a marker of proximal tubular damage. Unlike markers that primarily reflect filtration, KIM-1 provides information about epithelial injury and repair.

Urinary KIM-1 has been investigated in ischemic AKI, nephrotoxic injury, transplantation, critical illness, and chronic kidney disease. It may remain elevated during phases

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of ongoing tubular injury and has therefore attracted interest as both a diagnostic and prognostic marker. Some studies suggest that persistent elevations are associated with worse recovery.

Its limitations include variability among disease phenotypes and uncertainty about universal thresholds. KIM-1 may also reflect repair-related biology, so an elevated concentration should be interpreted as evidence of tubular response rather than a simple measure of irreversible damage [7,8].

Tissue Inhibitor of Metalloproteinases-2 and IGFBP7

TIMP-2 and IGFBP7 represent a different biomarker concept: cellular stress and G1 cell-cycle arrest. Injured tubular epithelial cells may temporarily halt proliferation to protect against division under unfavorable conditions. Urinary concentrations of these proteins can increase early, sometimes before conventional functional criteria identify AKI.

The combined urinary [TIMP-2]×[IGFBP7] assay has become one of the most clinically advanced biomarker approaches for AKI risk assessment. Evidence summarized in the current KDIGO 2026 public-review draft indicates moderate certainty for implementation in adults undergoing major surgery, with randomized trials suggesting that biomarker-guided kidney-protective strategies can reduce stage 2–3 AKI in selected postoperative populations. However, evidence is less mature in other settings, and the guideline emphasizes that performance varies by population.

Cutoff choice illustrates the trade-off between sensitivity and specificity. Lower thresholds identify more patients at risk but produce more false-positive results, whereas higher thresholds improve specificity but miss some patients. Thus, biomarker values should trigger structured clinical review rather than function as isolated diagnostic labels.

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

L-FABP is expressed in proximal tubular cells and participates in fatty-acid transport and oxidative-stress responses. Tubular ischemia and oxidative stress can increase urinary L-FABP. The marker has been studied particularly in postoperative and critically ill patients.

L-FABP may provide information that is complementary to markers such as NGAL because it reflects a partially different biological pathway. Its potential value lies in identifying early tubular stress and helping stratify patients after high-risk events. However, differences in assay methods and patient populations have limited standardization. Current evidence supports continued investigation rather than universal adoption.

N-Acetyl-β-D-Glucosaminidase (NAG)

NAG is a lysosomal enzyme abundant in proximal tubular cells. Because the molecule is relatively large and normally poorly filtered, urinary NAG elevation is often interpreted as evidence of tubular cell injury or lysosomal disruption. It has been explored in toxic, metabolic, and ischemic kidney injury.

NAG is attractive because it represents a mechanistically distinct tubular injury signal and may become abnormal before creatinine. Nevertheless, its clinical interpretation can be affected by chronic tubular disease and other sources of urinary enzyme activity. Standardized reference ranges and context-specific thresholds remain important barriers.

Interleukin-18 (IL-18) and Other Inflammatory Markers

IL-18 is a pro-inflammatory cytokine implicated in tubular inflammation. Urinary IL-18 has been evaluated as a marker of intrinsic tubular injury, particularly in critically ill and postoperative patients. Other inflammatory mediators, including monocyte chemotactic protein-1/CCL2 and CCL14, have also attracted attention.

These markers may be especially informative when inflammation contributes to progression. CCL14 is of interest because studies have associated urinary levels with persistent or progressive AKI and poor renal recovery. Such markers illustrate an emerging shift from simple injury detection toward phenotyping the biological pathway driving progression. The challenge is distinguishing kidney-specific inflammation from systemic inflammatory states.

Urinary Cystatin C and Low-Molecular-Weight Proteins

Urinary cystatin C can increase when proximal tubular reabsorption is impaired. Other low-molecular-weight proteins, including β2-microglobulin and α1-microglobulin, similarly provide information about tubular handling. These markers are therefore better viewed as indicators of tubular dysfunction than direct structural injury.

Their utility may be greatest in specific clinical contexts, including suspected proximal tubular dysfunction or disorders affecting tubular reabsorption. However, they have not demonstrated universal superiority over established biomarkers for early AKI detection, and guideline recommendations differ by setting.

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Urinary Angiotensinogen

Urinary angiotensinogen reflects activation of the intrarenal renin-angiotensin system and has been investigated as a marker of renal stress, particularly in hemodynamic and critical illness settings. Higher urinary concentrations have been associated with AKI risk in selected studies.

The biomarker is conceptually valuable because it links kidney injury with intrarenal hemodynamic signaling. However, additional validation is required to determine whether its measurement adds clinically meaningful information beyond established biomarkers and routine clinical variables.

MicroRNAs and Extracellular Vesicles

Molecular biomarkers are expanding the urinary diagnostic landscape. MicroRNAs are small non-coding RNAs that regulate gene expression and can reflect cellular responses to injury. Because they may be packaged in extracellular vesicles, urinary microRNAs can be relatively stable and may encode information about the cell of origin and biological pathway involved.

Extracellular vesicles, including exosomes, contain proteins, lipids, mRNA, microRNA, and other molecular signals. Their composition may provide a richer representation of renal cellular stress than a single soluble protein. Early studies have identified candidate signatures associated with AKI, CKD progression, diabetic kidney disease, and other renal disorders.

The principal challenge is translation. Isolation methods, normalization strategies, sequencing platforms, and candidate selection vary considerably. Large prospective studies and standardized analytical pipelines will be needed before molecular urinary signatures can become routine clinical tests.

Comparative Clinical Perspective

The major urinary biomarkers differ in what they measure. NGAL and KIM-1 primarily represent tubular injury; TIMP-2 and IGFBP7 reflect cellular stress and cell-cycle arrest; IL-18 and CCL14 reflect inflammatory biology; L-FABP reflects oxidative and metabolic stress; NAG reflects tubular lysosomal injury; and urinary cystatin C reflects impaired tubular reabsorption. This biological diversity is an advantage rather than a weakness because progressive kidney injury is heterogeneous.

Recent systematic evidence in critically ill adults found that NGAL and TIMP-2·IGFBP7 have among the more consistent performance profiles, although accuracy varies substantially between studies. A 2025 review reported NGAL sensitivity of approximately 65–89% and specificity of 60–85% across included ICU studies, while KIM-1 generally showed moderate performance and TIMP-2·IGFBP7 demonstrated a sensitivity-specificity trade-off dependent on cutoff.

No marker should be judged only by area under a receiver operating characteristic curve. A biomarker has clinical value when it changes decisions in a way that improves outcomes. This distinction is central to the next stage of biomarker research.

Role in Recognizing Progressive Kidney Injury

Early biomarker measurement could support a staged model of kidney injury. In the first stage, a high-risk exposure or clinical event occurs. Biomarkers may identify cellular stress before functional decline. In the second stage, serial biomarker measurements may indicate whether injury is resolving or persisting. In the third stage, persistent injury combined with declining filtration may identify patients at high risk for prolonged AKI, kidney replacement therapy, or transition toward chronic kidney disease.

Serial measurements may therefore be more informative than a single concentration. A rising trajectory may indicate active or worsening injury, whereas declining levels could accompany recovery. However, this concept requires validated biological and clinical thresholds for change. Biomarker kinetics are also influenced by urine dilution, timing, renal clearance, and the underlying cause of injury.

The most promising clinical application may be risk enrichment: identifying a subgroup in whom intensified kidney-protective care is justified. Such care could include medication review, avoidance of additional nephrotoxins, optimization of perfusion, careful fluid management, closer urine-output monitoring, and earlier nephrology involvement when appropriate.

Biomarker Panels and Multimodal Risk Prediction

Because kidney injury involves multiple biological pathways, combining biomarkers may outperform any single marker. A panel could theoretically include one marker of structural tubular injury, one marker of cellular stress, and one functional marker. For example, NGAL or KIM-1 could indicate tubular damage while TIMP-2·IGFBP7 identifies cell-cycle arrest and serum creatinine or cystatin C describes filtration.

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The Acute Disease Quality Initiative has emphasized that combinations of biomarkers may assist treatment planning. Future models may integrate biomarker concentrations with age, comorbidity, hemodynamics, exposure history, urine output, creatinine trajectory, and electronic health-record variables.

Artificial intelligence and machine learning could further support this approach, but model development should avoid overfitting and should demonstrate external validation. A highly accurate prediction model that does not improve clinical decisions or patient outcomes has limited practical value.

Challenges to Clinical Translation

Several barriers currently limit routine implementation. First, assay platforms and units are not always harmonized. Second, biomarker concentrations may vary with age, sex, baseline kidney function, inflammation, infection, and urine concentration. Third, different studies use different sampling times and AKI definitions, making direct comparison difficult.

Cost and reimbursement are additional considerations. Biomarker testing may be most valuable when it leads to an actionable intervention, but the intervention itself must be evidence-based. False-positive results may cause unnecessary monitoring or escalation, while false reassurance from a negative result can also be harmful. Current KDIGO guidance therefore emphasizes selective use, validated indications, and interpretation alongside clinical assessment.

Finally, many studies focus on prediction rather than clinical utility. The crucial question is not only whether a biomarker predicts AKI, but whether using that information changes care and improves outcomes.

Future Directions

Future research should move toward standardized, longitudinal, multimarker evaluation. Prospective multicenter studies should use harmonized sampling schedules, validated assays, prespecified thresholds, and clinically meaningful outcomes. Studies should also include diverse populations, including patients with chronic kidney disease, older adults, children, transplant recipients, and patients exposed to nephrotoxins.

Another priority is the development of biomarker-guided intervention trials. A positive biomarker should trigger a predefined clinical pathway, allowing investigators to determine whether earlier recognition actually prevents progression. Molecular approaches such as urinary extracellular vesicles, microRNA panels, proteomics, and metabolomics may eventually allow more precise phenotyping.

The future of urinary biomarkers is therefore unlikely to be a single universal test. Instead, the field is moving toward a layered system in which functional measures, structural injury markers, stress signals, inflammatory markers, and molecular signatures are integrated to characterize the timing and trajectory of kidney injury.

Discussion

The expanding urinary biomarker field reflects a fundamental change in how kidney injury is conceptualized. Traditional assessment asks whether kidney function has deteriorated. Biomarker-based assessment asks whether the kidney is being injured, stressed, inflamed, or failing to recover even before functional decline becomes obvious.

This distinction is clinically meaningful. A patient may have a normal or minimally changed serum creatinine while experiencing substantial tubular stress. Conversely, an elevated biomarker does not necessarily mean irreversible injury. Biomarkers should therefore be interpreted as biological signals within a temporal and clinical framework.

Among current candidates, NGAL has substantial evidence and broad clinical interest, KIM-1 provides a relatively specific tubular injury signal, and TIMP-2·IGFBP7 has advanced furthest toward biomarker-guided prevention in selected adult surgical populations. CCL14 and other inflammatory markers may become important for identifying persistent or progressive injury, while molecular platforms may eventually provide more individualized phenotypes.

Importantly, the current evidence does not justify replacing creatinine and urine output with biomarkers. Instead, biomarkers can complement conventional assessment by filling the diagnostic gap between exposure and functional decline. This complementary strategy is consistent with the emerging KDIGO framework that incorporates structural biomarkers into the broader AKI/AKD continuum.

For progressive kidney injury, serial measurement and biomarker combinations are likely to be more informative than isolated values. The ultimate objective should be prevention of clinically important outcomes rather than earlier labeling alone.

Conclusion

Emerging urinary biomarkers offer an important opportunity to recognize kidney injury before conventional

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functional deterioration becomes evident. NGAL, KIM-1, L-FABP, NAG, IL-18, TIMP-2, IGFBP7, CCL14, urinary cystatin C, and molecular biomarkers each capture different aspects of renal pathobiology. Current evidence supports their potential for early risk stratification, but no single biomarker is sufficiently universal to replace standard clinical assessment.

The most promising future approach is an integrated biomarker strategy combining structural injury, cellular stress, inflammation, and filtration markers with clinical risk factors and serial measurements. Translation into routine practice will depend on assay standardization, validated thresholds, cost-effectiveness, diverse population studies, and—most importantly—interventional trials demonstrating that biomarker-guided care improves patient outcomes. As kidney medicine moves toward earlier detection and precision risk stratification, urinary biomarkers may become a central component of proactive kidney protection.

Declarations

Conflict of Interest

The author declares no conflict of interest related to this manuscript.

Funding

No specific funding was received for the preparation of this manuscript.

Author Contribution

The author contributed to the conception, literature synthesis, drafting, and final preparation of the manuscript.

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