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BEYOND CREATININE: THE ROLE OF EMERGING BIOMARKERS IN EARLY DETECTION OF ACUTE KIDNEY INJURY IN ADULTS: A SYSTEMATIC REVIEW

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ABSTRACT

Acute kidney injury (AKI) is a common clinical syndrome associated with increased morbidity, mortality, length of hospitalization, and long-term risk of chronic kidney disease. In routine practice, AKI is still diagnosed primarily by changes in serum creatinine concentration and urine output. Although these criteria are standardized and clinically useful, they are imperfect markers of early kidney injury because creatinine rises only after a fall in filtration has occurred and urine output is influenced by hemodynamics, medications, fluid balance, and measurement accuracy. This systematic literature review evaluates the role of emerging biomarkers in the early detection and risk stratification of AKI in adults, with particular emphasis on neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), cystatin C, and the cell-cycle arrest biomarker combination tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7]). The reviewed literature suggests that biomarkers may identify tubular stress or injury earlier than conventional criteria, support risk stratification in selected high-risk populations, and help distinguish functional decline from structural damage. However, heterogeneity of populations, assay platforms, timing of sampling, thresholds, and reference standards limits routine implementation. Biomarkers are best understood as adjuncts to clinical assessment rather than replacements for standard diagnostic criteria.

KEYWORDS

Acute Kidney Injury, AKI Biomarkers, NGAL, KIM-1, TIMP-2, IGFBP7

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Introduction

Acute kidney injury (AKI) is a heterogeneous clinical syndrome characterized by an abrupt decline in kidney function. It is encountered across emergency departments, internal medicine wards, surgical units, intensive care units, and perioperative settings. AKI is clinically important not only because it may progress to life-threatening electrolyte, acid-base, and volume disturbances, but also because even apparently mild episodes are associated with increased mortality, longer hospitalization, higher costs of care, and an increased risk of chronic kidney disease. The clinical relevance of AKI therefore extends beyond nephrology and critical care; it is a common problem in general hospital medicine and a frequent marker of systemic illness severity (Ronco et al., 2019).

The modern definition of AKI has been shaped by the need for standardized diagnostic and staging criteria. The KDIGO framework defines AKI by an increase in serum creatinine, a relative rise from baseline creatinine, or reduced urine output. These criteria have improved epidemiological research, enabled comparison across studies, and encouraged earlier recognition of clinically apparent kidney dysfunction. However, the same criteria also reveal a fundamental limitation: AKI is commonly diagnosed after functional impairment is already measurable rather than at the moment when kidney injury begins (Kellum & Lameire, 2013).

Serum creatinine remains the most widely used laboratory marker of kidney function in hospitalized adults. It is inexpensive, routinely available, standardized in most laboratories, and familiar to clinicians. Nevertheless, creatinine is an indirect marker of glomerular filtration rather than a direct marker of tubular injury. Its concentration is influenced by age, sex, muscle mass, diet, hydration status, hepatic function, tubular secretion, and volume of distribution. In acute illness, fluid accumulation may dilute serum creatinine and obscure the true severity of kidney injury. In patients without a known baseline creatinine, diagnosis often requires estimation of previous renal function, which may lead to both overdiagnosis and underdiagnosis. These limitations are especially relevant in frail older adults, septic patients, postoperative patients, and critically ill individuals with rapidly changing physiology (Ronco et al., 2019; Ostermann et al., 2020).

Urine output is another cornerstone of AKI diagnosis, but it also has practical and conceptual limitations. Oliguria may reflect renal hypoperfusion, vasopressor exposure, obstruction, neurohormonal activation, diuretic use, or inadequate fluid intake rather than intrinsic structural kidney injury. Conversely, nonoliguric AKI may be missed if clinicians rely primarily on urine volume. Accurate hourly urine output monitoring often requires a urinary catheter, which is not appropriate or feasible for all hospitalized patients. Documentation may be incomplete outside the ICU, and fluid balance charts may be inaccurate. As a result, urine output criteria are valuable but cannot reliably distinguish early kidney stress from established tubular damage in all settings (Kellum & Lameire, 2013).

These diagnostic limitations have generated sustained interest in novel AKI biomarkers. Unlike serum creatinine and urine output, biomarkers may reflect different biological dimensions of kidney injury: tubular damage, inflammation, oxidative stress, impaired filtration, cell-cycle arrest, or renal repair. Some markers, such as NGAL, KIM-1, IL-18, and L-FABP, are associated with tubular injury or inflammatory pathways. Cystatin C reflects filtration and may change earlier than creatinine in some contexts. The combination [TIMP-2]*[IGFBP7] reflects cell-cycle arrest and renal tubular stress, and has been studied extensively in critically ill and perioperative populations (Kashani et al., 2013; Ostermann et al., 2020).

The promise of biomarkers is clinically attractive. A biomarker that rises before creatinine could identify patients at high risk of AKI when preventive measures are still possible, guide avoidance of nephrotoxins, support hemodynamic optimization, improve timing of nephrology consultation, and allow better selection of patients for clinical trials. Biomarker-guided bundles have already been tested in selected postoperative high-risk populations, suggesting that early risk identification can be linked to actionable kidney-protection strategies (Meersch et al., 2017; Zarbock et al., 2021).

However, enthusiasm must be balanced by caution. AKI is not a single disease but a syndrome caused by multiple pathways, including ischemia, sepsis, nephrotoxicity, venous congestion, inflammation, obstruction, and surgery-associated injury. A biomarker that performs well after cardiac surgery may not perform identically in sepsis, trauma, cirrhosis, or drug-induced kidney injury. Moreover, a biomarker may detect injury without immediate functional decline, which creates interpretive uncertainty. The central clinical question is therefore not whether biomarkers rise earlier than creatinine, but whether their use improves decisions, outcomes, and resource allocation in real patients.

This systematic review focuses on emerging biomarkers for early AKI detection in adults. The aim is to synthesize clinically relevant evidence regarding biomarker categories, diagnostic performance, potential clinical applications, and barriers to implementation. Particular attention is given to the limitations of conventional diagnostic criteria, the distinction between functional and damage biomarkers, the most frequently studied candidate biomarkers, and the practical conditions under which biomarkers may add value to standard care.

Methodology

This manuscript was prepared as a systematic literature review using principles derived from the PRISMA 2020 statement. The review was not registered in PROSPERO. The objective was to identify and synthesize contemporary evidence regarding the use of emerging biomarkers for early detection and clinical risk stratification of AKI in adults. Because the available literature includes heterogeneous study designs, populations, biomarkers, thresholds, and clinical settings, findings were synthesized descriptively rather than by formal meta-analysis.

A literature search was conducted in PubMed/MEDLINE and PubMed Central. The search strategy combined terms related to AKI, early diagnosis, conventional diagnostic limitations, and specific biomarkers. Search terms included: "acute kidney injury", "AKI", "early detection", "biomarker", "serum creatinine", "urine output", "NGAL", "kidney injury molecule-1", "KIM-1", "interleukin-18", "IL-18", "L-FABP", "cystatin C", "TIMP-2", "IGFBP7", "cell cycle arrest", "critical care", "cardiac surgery", and "biomarker-guided intervention". Boolean operators AND and OR were used to combine terms. Reference lists of relevant reviews, consensus statements, and clinical trials were also screened for additional eligible publications.

Eligible publications included systematic reviews, meta-analyses, consensus statements, clinical practice guideline summaries, prospective observational studies, randomized trials, and clinically oriented reviews involving adult patients or mixed populations with clearly relevant adult data. Priority was given to studies indexed in PubMed, available through PubMed Central, or published in established peer-reviewed journals. Studies were included if they addressed early AKI detection, biomarker diagnostic accuracy, risk

prediction, prognostic value, or biomarker-guided management. Publications focused exclusively on pediatric populations, animal studies, case reports, conference abstracts without full manuscripts, and articles not directly related to AKI biomarkers were excluded.

Data extracted from selected publications included study design, population, clinical setting, biomarkers evaluated, timing of biomarker measurement, comparator or reference standard, diagnostic or prognostic outcomes, and major limitations. The analysis focused on adult clinical applicability rather than mechanistic laboratory detail. Biomarkers were grouped into functional markers, damage markers, inflammatory markers, stress markers, and multimarker approaches. The quality of evidence was interpreted pragmatically, with emphasis on consistency across studies, study design, population heterogeneity, and potential impact on clinical decision-making.

The main outcomes of interest were: (1) ability of biomarkers to detect or predict AKI earlier than serum creatinine; (2) usefulness in risk stratification; (3) relationship with clinically important outcomes such as severe AKI, kidney replacement therapy, persistent AKI, mortality, or renal recovery; and (4) barriers to implementation in routine hospital practice. Due to heterogeneity in AKI definitions, sampling timepoints, biomarker thresholds, and laboratory platforms, pooled estimates were not recalculated in this review.

Table 1. Limitations of Conventional AKI Diagnostic Criteria

Criterion	Clinical usefulness	Main limitations
Serum creatinine	Widely available functional marker used in KDIGO staging and routine clinical monitoring.	Delayed rise after injury, dependence on muscle mass and volume status, need for baseline value, dilution by fluid overload, limited information about structural injury.
Urine output	May detect hemodynamic deterioration early and is useful in ICU monitoring.	Nonspecific oliguria, influence of diuretics and fluid balance, inaccurate measurement outside ICU, catheter-related limitations, inability to distinguish adaptive physiology from tubular damage.
Estimated baseline kidney function	Allows AKI classification when previous creatinine is unavailable.	Imputation may misclassify patients, especially older adults and patients with undiagnosed CKD.

Note. AKI = acute kidney injury; CKD = chronic kidney disease; ICU = intensive care unit.

Results

The reviewed literature consistently identifies serum creatinine and urine output as necessary but incomplete tools for AKI recognition. Creatinine is widely available and remains embedded in clinical guidelines, but it is a delayed functional marker. A measurable increase often occurs after substantial changes in glomerular filtration have already developed. In rapidly evolving AKI, this delay may create a diagnostic window during which kidney injury is biologically present but not yet evident by standard criteria. This window is particularly important in settings where preventive measures, avoidance of nephrotoxins, and hemodynamic optimization may alter the course of injury.

Urine output criteria may detect AKI earlier than creatinine in some patients, especially in critical care. However, oliguria is nonspecific and may reflect transient adaptive physiology rather than structural kidney damage. Measurement accuracy is highly setting-dependent. Intensive care units can measure hourly urine output more precisely, whereas general wards often rely on intermittent or estimated volumes. Diuretics, fluid restriction, urinary catheter practices, and documentation errors may all distort interpretation. Therefore, conventional criteria define clinically apparent AKI but do not fully capture early kidney stress or subclinical tubular injury.

Functional biomarkers such as cystatin C aim to improve early assessment of filtration. Cystatin C is less dependent on muscle mass than creatinine and may respond more rapidly to changes in glomerular filtration. It has been studied as both a diagnostic and prognostic marker in AKI. However, cystatin C is still primarily a marker of function rather than direct tubular damage. It may be influenced by inflammation, corticosteroid exposure, thyroid status, and other nonrenal factors. Its availability and cost also vary between healthcare systems. Consequently, cystatin C may complement creatinine but does not by itself solve the problem of differentiating functional decline from structural injury.

NGAL is one of the most widely studied AKI biomarkers. It is expressed in injured tubular epithelium and can be measured in urine or plasma. Many studies suggest that NGAL rises earlier than serum creatinine

after renal insult, particularly in cardiac surgery, critical illness, and emergency settings. A large comparative meta-analysis found that NGAL-based measurements, especially urinary NGAL and urinary NGAL normalized to creatinine, showed strong predictive accuracy for hospital-acquired AKI across clinical settings (Pan et al., 2022). This supports the concept that tubular injury markers can improve early risk recognition.

Despite this promise, NGAL has limitations that restrict universal implementation. Plasma NGAL may rise in systemic inflammation, sepsis, infection, and neutrophil activation, reducing renal specificity. Urinary NGAL may be affected by urinary tract infection, chronic kidney disease, and underlying tubular pathology. Cutoff values differ across studies, and assay standardization remains an issue. In addition, the clinical meaning of an isolated NGAL elevation without a creatinine rise is not always clear. Such a finding may indicate subclinical injury, increased susceptibility to subsequent AKI, or nonspecific inflammatory activity. Therefore, NGAL is most useful when interpreted in context rather than as a stand-alone diagnostic label.

KIM-1 is a tubular injury marker expressed after proximal tubular damage. It is biologically attractive because proximal tubular injury is central to many AKI phenotypes, including ischemic and nephrotoxic injury. Studies have evaluated urinary KIM-1 for early AKI detection and prognostication. KIM-1 may be particularly relevant in drug-induced or toxic tubular injury, but its performance is variable across clinical populations. Compared with NGAL, KIM-1 often appears later in the course of injury, which may limit its use as a very early marker in some settings. It may also be elevated in chronic kidney disease and other forms of ongoing tubular pathology.

IL-18 is an inflammatory cytokine associated with ischemic tubular injury. It has been investigated in cardiac surgery, critical illness, and transplant-related kidney injury. Its biological link to inflammation makes it potentially informative, especially in inflammatory AKI phenotypes. However, this same feature creates specificity problems. Systemic inflammation, sepsis, and comorbid inflammatory conditions may influence IL-18 concentrations. As a result, IL-18 is unlikely to serve as a universal stand-alone diagnostic marker. Its value may be greater when combined with other markers that represent complementary biological pathways.

L-FABP is a marker associated with tubular stress, hypoxia, and oxidative injury. It may reflect early tubular response to ischemia and has been studied in cardiac surgery, contrast exposure, and critical illness. Some studies suggest that L-FABP can help identify patients at risk for AKI before creatinine rises. However, evidence is less extensive than for NGAL and [TIMP-2]*[IGFBP7]. Variability in assay methods and patient populations makes it difficult to establish universal thresholds. Like other tubular biomarkers, L-FABP is best interpreted as one component of a broader risk assessment strategy.

The combination [TIMP-2]*[IGFBP7] represents a different biomarker concept. These proteins are associated with G1 cell-cycle arrest, a protective cellular response to stress. Their product has been studied as a urinary marker of tubular stress in critically ill patients and perioperative populations. The Sapphire study identified and validated [TIMP-2]*[IGFBP7] as a predictor of moderate to severe AKI within a short time window, with performance superior to several other candidate biomarkers in that study (Kashani et al., 2013). Subsequent validation and clinical studies supported its use for near-term risk stratification rather than as a direct measure of established loss of filtration.

Table 2. Major Categories of Emerging AKI Biomarkers

Biomarker group	Examples	Primary biological signal	Clinical interpretation
Functional markers	Serum creatinine, cystatin C	Change in glomerular filtration	Useful for functional staging, but may not directly indicate structural injury.
Tubular injury markers	NGAL, KIM-1, L-FABP	Tubular epithelial injury or stress	May rise earlier than creatinine; specificity varies by clinical context.
Inflammatory markers	IL-18	Inflammatory tubular response	Potentially useful in ischemic or inflammatory phenotypes but may be confounded by systemic inflammation.
Cell-cycle arrest markers	[TIMP-2]*[IGFBP7]	Tubular stress and G1 cell-cycle arrest	Useful for near-term risk stratification in selected high-risk populations.
Multimarker panels	Combinations of function, injury, stress, and inflammatory markers	Multiple AKI pathways	May improve phenotyping but require validation and clear action pathways.

Note. NGAL = neutrophil gelatinase-associated lipocalin; KIM-1 = kidney injury molecule-1; L-FABP = liver-type fatty acid-binding protein; IL-18 = interleukin-18; TIMP-2 = tissue inhibitor of metalloproteinases-2; IGFBP7 = insulin-like growth factor-binding protein 7.

The clinical appeal of [TIMP-2]*[IGFBP7] lies in its potential actionability. A positive test may identify patients who appear clinically stable but are biologically vulnerable to AKI. In postoperative or ICU settings, this can trigger avoidance of nephrotoxins, optimization of hemodynamics, glycemic control, careful fluid management, and closer monitoring. The PrevAKI trial demonstrated that a KDIGO-based care bundle applied to high-risk cardiac surgery patients identified by urinary [TIMP-2]*[IGFBP7] reduced postoperative AKI in the single-center setting (Meersch et al., 2017). The later multicenter PrevAKI trial tested a similar biomarker-guided approach across multiple centers, supporting the feasibility of linking biomarker positivity to structured prevention strategies (Zarbock et al., 2021).

Meta-analytic data suggest that [TIMP-2]*[IGFBP7] has useful diagnostic and prognostic performance, particularly in critical care and postoperative populations. However, the marker should not be interpreted as a general screening test for all hospitalized adults. It performs best in populations with meaningful pretest risk and a clear plan for intervention after a positive result. Its use in low-risk populations may increase cost and uncertainty without improving outcomes. This point is central: biomarker value depends not only on analytical performance but also on clinical workflow, pretest probability, and availability of an evidence-informed response.

Multimarker approaches attempt to address AKI heterogeneity by combining markers of filtration, tubular injury, inflammation, stress, and repair. Conceptually, such panels may distinguish functional AKI, structural injury, subclinical AKI, and maladaptive recovery more accurately than any single biomarker. For example, a patient with preserved creatinine but high tubular injury markers may have subclinical AKI, whereas a patient with creatinine elevation but low injury markers may have predominantly functional or hemodynamic impairment. ADQI consensus statements emphasize that biomarker interpretation may be improved by separating functional change from tissue damage (Ostermann et al., 2020).

Evidence also supports the prognostic relevance of biomarkers. Some biomarkers are associated with severe AKI, persistent AKI, kidney replacement therapy, mortality, or incomplete renal recovery. This is clinically important because early diagnosis alone is not enough; clinicians need to identify which patients are likely to deteriorate and which may recover with supportive care. Biomarkers may help enrich clinical trials by selecting patients at high risk before irreversible damage develops. They may also support follow-up planning after hospital discharge by identifying individuals at risk for AKI-to-CKD transition.

Despite progress, several barriers prevent routine adoption. First, the reference standard remains imperfect. Most biomarker studies define AKI using creatinine and urine output, but these are precisely the markers that biomarkers are intended to improve upon. This creates circularity: a marker that detects true early tubular injury may appear falsely inaccurate if creatinine never rises. Second, sampling timepoints differ widely. A biomarker may perform well if measured four hours after cardiac surgery but poorly if measured at an unrelated time in septic shock. Third, thresholds vary by assay, population, and outcome. Fourth, biomarker studies differ in whether they assess prediction, diagnosis, staging, prognosis, or response to therapy.

Another important finding is that biomarker implementation requires clinical decision support. A test result without a clear action plan may not change patient outcomes. Biomarker-guided strategies are most convincing when embedded in bundles of care: medication review, avoidance of nephrotoxins, hemodynamic optimization, fluid assessment, monitoring frequency, and timely specialist consultation. Without such pathways, biomarkers may merely increase diagnostic complexity. This is why the shift from biomarker discovery to biomarker-guided management is a key theme in the literature.

Electronic alerts are another strategy for improving AKI recognition. Most current alert systems rely on changes in creatinine, but future systems may integrate risk prediction, urine output, exposure to nephrotoxins, hemodynamic instability, and biomarker results. Laboratory-based and electronic health record-based alerts may reduce missed recognition, but alert fatigue and inappropriate triggering remain concerns. The most promising future model is probably not a single biomarker or a single alert, but a multimodal system that combines clinical context with laboratory, functional, injury, and stress markers.

Discussion

The findings of this review suggest that AKI biomarker research has moved beyond the simple question of whether a biomarker rises earlier than creatinine. The more important clinical question is how biomarkers can be used to improve decisions. Creatinine and urine output remain necessary because they define functional impairment and guide staging, drug dosing, fluid management, and kidney replacement therapy decisions. However, they are insufficient for early injury detection. Biomarkers may fill this gap by identifying patients with kidney stress or tubular damage before overt functional decline.

A clinically useful way to interpret AKI biomarkers is to divide them into functional and damage-related categories. Functional markers, such as creatinine and cystatin C, estimate filtration. Damage markers, such as NGAL, KIM-1, IL-18, and L-FABP, reflect structural or inflammatory tubular injury. Stress markers, particularly [TIMP-2]*[IGFBP7], may indicate cellular response to injury before irreversible dysfunction occurs. This framework helps explain why biomarker results may appear discordant. A patient may have damage without loss of function, loss of function without overt injury, or both. Such discordance is not necessarily a weakness; it may reveal clinically meaningful AKI phenotypes that conventional criteria conceal.

The concept of subclinical AKI is particularly important. Patients with elevated injury biomarkers but without creatinine-defined AKI may still have worse outcomes than biomarker-negative patients in some studies. This suggests that conventional diagnostic criteria may underestimate the biological burden of kidney injury. However, the management of subclinical AKI remains uncertain. Clinicians may intensify monitoring and avoid nephrotoxins, but there is no universally accepted treatment triggered by a biomarker alone. Therefore, biomarker positivity should currently be interpreted as a risk signal rather than as an independent disease category requiring a specific therapy.

NGAL has the advantage of extensive study across multiple settings. Its early rise makes it useful for risk prediction, and meta-analytic evidence suggests favorable performance in hospital-acquired AKI. Nevertheless, NGAL is sensitive to systemic inflammation, which is common in the same populations at risk for AKI. This limitation is especially relevant in sepsis, where neutrophil activation, infection, and tubular injury may coexist. The challenge is not that NGAL is uninformative, but that it is biologically broad. It may be most valuable when combined with clinical context and other markers rather than interpreted as a kidney-specific yes-or-no test.

KIM-1 and L-FABP provide additional tubular information but are less established in routine adult hospital practice. KIM-1 may be useful in proximal tubular injury and nephrotoxic exposure, whereas L-FABP may reflect hypoxic or oxidative tubular stress. IL-18 adds inflammatory information. These markers illustrate the heterogeneity of AKI biology, but none has achieved universal adoption. Their future use may lie in panels designed to identify specific AKI phenotypes rather than in broad screening of unselected patients.

The cell-cycle arrest biomarkers [TIMP-2]*[IGFBP7] have one of the clearest clinical implementation pathways. They are intended for risk assessment in critically ill or postoperative patients rather than broad diagnostic confirmation. This distinction matters. A positive result can identify patients at high risk of imminent moderate to severe AKI, creating an opportunity for preventive bundles. The PrevAKI studies demonstrate the logic of this model: biomarker testing becomes clinically relevant when it is linked to a structured intervention. This approach is more compelling than biomarker measurement without a response plan.

Biomarker-guided prevention is also consistent with the broader pathophysiology of AKI. Many forms of AKI evolve through a phase of vulnerability before sustained loss of filtration. During this phase, additional insults such as hypotension, nephrotoxins, contrast exposure, hyperglycemia, or venous congestion may push the kidney toward clinically apparent injury. If biomarkers identify this vulnerable state, they may support preventive actions. However, the effectiveness of such strategies depends on whether clinicians can modify exposures quickly enough and whether the intervention bundle is applied reliably.

The limitations of existing evidence must be acknowledged. Many studies are observational, use different AKI definitions, and measure biomarkers at different times relative to injury. Cardiac surgery provides a relatively controlled model because the timing of renal insult is known. In sepsis, emergency medicine, and general wards, injury timing is much less clear. A biomarker measured at hospital admission may represent injury that occurred hours or days earlier, making diagnostic interpretation difficult. This explains why results from cardiac surgery cannot be directly transferred to all hospitalized adults.

Another limitation is the use of creatinine-defined AKI as the reference standard. If creatinine is delayed and insensitive, using it as the endpoint may underestimate the accuracy of biomarkers that detect injury earlier. Conversely, biomarkers may identify biological changes that do not progress to clinically important AKI. Both possibilities complicate interpretation. Future studies should incorporate patient-centered outcomes such as

persistent kidney dysfunction, need for kidney replacement therapy, mortality, MAKE events, and CKD progression rather than relying only on short-term creatinine changes.

Clinical adoption also depends on feasibility and cost. A biomarker that requires specialized laboratory processing may not be useful in urgent decision-making if turnaround time is long. Point-of-care or rapidly available platforms are more likely to influence management. In addition, hospitals need protocols specifying when to order the test, how to interpret the result, and what actions should follow. Without such pathways, biomarker testing can increase cost without improving care. Health economic analyses are therefore needed, especially for ward-based and emergency department use.

The relationship between biomarkers and electronic decision support deserves attention. Traditional AKI alerts based only on creatinine changes may detect AKI after injury has already occurred. Predictive models using electronic health record data may identify risk earlier, but they may also generate false positives or alert fatigue. Biomarkers could improve the specificity of risk prediction if integrated with clinical variables such as age, baseline kidney function, sepsis, surgery, nephrotoxin exposure, hemodynamics, and fluid balance. However, such integrated systems must be prospectively tested before widespread implementation.

From a practical clinical perspective, biomarkers should currently be considered most useful in selected high-risk settings: major surgery, cardiac surgery, sepsis, critical illness, nephrotoxic drug exposure, and patients with uncertain renal reserve. In these contexts, early identification of kidney stress may change monitoring and preventive behavior. In low-risk populations, routine biomarker screening is less clearly justified. This targeted approach aligns with the principle that diagnostic tests are most useful when pretest probability and post-test actions are clearly defined.

Table 3. Potential Clinical Applications and Barriers to Implementation

Clinical context	Potential biomarker role	Possible action after positive result	Key limitation
Cardiac or major surgery	Early identification of postoperative kidney stress	KDIGO bundle, hemodynamic optimization, nephrotoxin review, intensified monitoring	Evidence strongest in selected high-risk surgical populations.
Critical illness and sepsis	Risk stratification and detection of tubular stress/injury	Fluid and vasopressor reassessment, antimicrobial and nephrotoxin review, closer urine output and creatinine monitoring	Inflammation and multiorgan failure may affect biomarker specificity.
Emergency department	Early risk identification before admission or deterioration	Disposition planning, medication review, repeat laboratory testing	Variable baseline kidney function and uncertain timing of injury.
Drug-induced kidney injury risk	Detection of tubular damage before creatinine rises	Stop or adjust nephrotoxins, monitor drug levels, hydrate when appropriate	No universal thresholds for all nephrotoxins.
General wards	Enhanced recognition of high-risk patients	Electronic alert plus clinical review pathway	Cost, turnaround time, low pretest probability, and workflow limitations.

Note. A biomarker result is most useful when linked to a predefined clinical response pathway.

The role of biomarkers in differentiating AKI etiologies is promising but still limited. Clinicians often need to distinguish prerenal physiology, acute tubular injury, obstruction, glomerulonephritis, interstitial nephritis, and chronic kidney disease with superimposed acute dysfunction. Biomarkers may eventually contribute to this differential diagnosis, especially when combined with urine microscopy, clinical history, medication review, imaging, and serological tests. At present, however, no biomarker panel can replace careful clinical evaluation. Biomarkers should therefore be used to refine, not replace, bedside reasoning.

An additional clinical implication concerns medication safety. AKI often develops in patients receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, aminoglycosides, vancomycin, amphotericin B, iodinated contrast agents, or combinations of nephrotoxic exposures. Conventional diagnosis may occur only after the injury has progressed enough to change creatinine. Earlier risk signals from biomarkers could theoretically support medication review before severe dysfunction develops. However, this approach requires careful stewardship. Automatically stopping all

potentially nephrotoxic drugs after a biomarker rise may cause harm if essential therapies are withheld. The role of biomarkers should therefore be to trigger structured reassessment rather than reflexive discontinuation.

Another area of interest is sepsis-associated AKI. Sepsis is one of the most frequent and clinically severe contexts in which AKI occurs. The pathophysiology involves inflammation, microcirculatory dysfunction, endothelial injury, tubular metabolic adaptation, and immune-mediated mechanisms rather than simple renal hypoperfusion alone. Biomarkers may help identify patients in whom kidney stress is already present before creatinine-defined AKI develops. Yet sepsis also illustrates the interpretive difficulty of biomarkers: systemic inflammation can raise some markers independently of kidney-specific damage, while fluid resuscitation can dilute creatinine and delay conventional recognition. In this setting, multimarker interpretation and serial trends may be more informative than a single isolated value.

Postoperative AKI provides a contrasting example. In cardiac surgery and major surgery, the timing of the renal insult is more predictable, making biomarker measurement easier to standardize. This partly explains why many supportive data for [TIMP-2]*[IGFBP7], NGAL, and other markers come from perioperative cohorts. Biomarker elevation shortly after surgery may identify patients for intensified monitoring and kidney-protection bundles during the period when injury is still evolving. Nevertheless, postoperative patients differ substantially by baseline kidney function, bypass duration, hemodynamic instability, inflammation, bleeding, transfusion burden, and vasopressor exposure. Thus, even in this comparatively controlled setting, biomarkers must be interpreted within a broader clinical model.

A further issue is communication between laboratory medicine and clinical teams. For a biomarker to be adopted safely, clinicians must understand what biological process it reflects, what time window it predicts, what threshold is used, and what action is recommended. Misinterpretation may occur if a biomarker is treated as equivalent to creatinine or if a positive result is understood as definitive AKI rather than increased risk. Reports should ideally include interpretive comments, local reference thresholds, and links to institutional protocols. This is particularly important for junior clinicians, who may be familiar with creatinine-based AKI staging but less familiar with functional, damage, and stress biomarker frameworks.

The reviewed literature also suggests that AKI biomarkers may have research value even before universal clinical implementation. Biomarkers can enrich clinical trial populations by selecting patients who are more likely to develop AKI or severe outcomes. This enrichment is important because many previous AKI therapeutic trials have failed partly because enrolled populations were biologically heterogeneous or because treatment began after injury was established. Biomarker-positive patients may represent a group in whom preventive or early therapeutic interventions are more plausible. Therefore, biomarkers may accelerate AKI research by improving patient selection and endpoint definition.

Equity and access should not be ignored. Advanced biomarkers may initially be available mainly in tertiary centers, cardiac surgical units, and well-resourced ICUs. If biomarker-guided care proves clinically useful, unequal access could widen disparities in AKI prevention. On the other hand, if biomarker testing is targeted to high-risk patients and linked to simple preventive bundles, it may reduce avoidable complications. Future implementation studies should therefore assess not only diagnostic accuracy but also cost-effectiveness, workflow impact, and accessibility in different hospital systems.

In summary, the evidence supports a balanced interpretation. Biomarkers are not magic substitutes for clinical assessment, urine microscopy, hemodynamic evaluation, imaging when obstruction is suspected, or careful medication review. Their value lies in adding biological information that conventional criteria lack. The most clinically useful question is not whether a biomarker can label a patient as having AKI, but whether it identifies a modifiable risk state earlier than current practice. This distinction should guide future protocols, education, and research design.

This review has limitations. The synthesis was based on published English-language literature available through PubMed/MEDLINE and PubMed Central, and no new meta-analysis was performed. Heterogeneity across studies prevented direct quantitative comparison of all biomarkers. Some newer biomarkers, including CCL14, DKK3, proenkephalin, suPAR, and cell-free nucleic acid markers, were discussed only briefly because evidence is still evolving. In addition, many studies focus on ICU or postoperative populations, so conclusions may not apply equally to general internal medicine wards or outpatient settings.

Future research should prioritize implementation rather than discovery alone. Important unanswered questions include which adult populations benefit most from biomarker testing, which thresholds should trigger action, whether biomarker-guided bundles improve long-term outcomes, and how biomarkers should be integrated into electronic clinical decision support. Studies should also examine equity and accessibility. If novel biomarkers are available only in highly resourced centers, their population-level impact may be limited. Conversely, if they can reduce severe AKI, dialysis, and long-term CKD progression, they may become valuable components of hospital safety systems.

Conclusions

Emerging biomarkers offer a biologically richer approach to AKI detection than conventional creatinine and urine output criteria alone. Serum creatinine and urine output remain essential for defining and staging AKI, but they are delayed, nonspecific, and vulnerable to measurement limitations. Biomarkers such as NGAL, KIM-1, IL-18, L-FABP, cystatin C, and [TIMP-2]*[IGFBP7] may identify kidney stress or tubular injury earlier, particularly in high-risk adult populations.

The current evidence supports biomarkers as adjunctive tools for risk stratification rather than replacements for clinical assessment. Their greatest value appears to be in settings where early risk recognition can trigger actionable kidney-protection bundles. The strongest implementation model is therefore not isolated biomarker measurement, but biomarker-guided clinical pathways integrated with hemodynamic optimization, nephrotoxin avoidance, close monitoring, and decision support.

Routine use is limited by heterogeneity of AKI phenotypes, inconsistent thresholds, assay variability, imperfect reference standards, cost, and uncertain impact on patient-centered outcomes. Future research should focus on validating biomarker-guided strategies in diverse adult populations and determining whether early detection translates into reduced severe AKI, kidney replacement therapy, mortality, and long-term chronic kidney disease progression.

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