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Beyond Serum Creatinine: Emerging Biomarkers for Early Detection and Prognosis of Acute Kidney Injury

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ABSTRACT
The diagnosis of acute kidney injury (AKI) is a major cause of morbidity and mortality as traditional markers such as serum creatinine and urine output only reflect kidney functional decline at a time when these kidneys have already sustained some degree of renal stress and injury. Emerging biomarkers provide a more biologically meaningful option by measuring damage to the tubules, cellular stress, changes in filtration, inflammation, metabolic disturbance and failure to recover at various stages of AKI. This review aims to present the latest evidence of the use of conventional and emerging biomarkers for early detection, risk stratification, clinical decision making and prognostic assessment. Special focus will be on neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C, liver-type fatty acid-binding protein, TIMP-2, IGFBP7, CCL14, soluble urokinase plasminogen activator receptor, proenkephalin, microRNAs, and metabolomic signatures, along with urinary oxygen partial pressure. Existing data suggest that these markers have the potential to supplement serum creatinine to identify subclinical injury, distinguish between reversible and irreversible injury, assess the risk of kidney replacement therapy, and predict renal recovery and kidney disease progression. The performance is however dependent on clinical setting, assay method, when the measurement is taken and patient heterogeneity. Multimarker strategies and serial biomarker profiling might therefore offer a greater diagnostic and prognostic ability than single markers. Standardization of assays, clinically validated thresholds, multicenter evaluation and demonstration of benefit of using biomarker-driven management for meaningful outcomes will be required for future progress. Combining functional, structural, stress, and molecular markers with clinical monitoring could potentially allow for earlier recognition, more accurate prognosis, personalized monitoring, and improved short and long-term outcomes in AKI in a variety of acute care and critical care settings around the world.

Keywords: Acute kidney injury; Biomarkers; Early detection; Risk stratification; Prognosis

1. Introduction

Acute kidney injury (AKI) encompasses a spectrum of clinical situations where kidney function is rapidly lost (over hours – days) and can vary from mild, reversible loss of function to severe renal failure in the acute setting, for which kidney replacement therapy is required. Often seen in the critically ill, septic, postoperative, and hemodynamically unstable patient, and linked to longer hospital stays, death and risk of chronic kidney disease. This has led to greater interest in ways of detecting renal injury before the usual markers of abnormal values, as well as ways of identifying those at highest risk of progression and/or poor outcome.

The ongoing evaluation of AKI is still largely dependent on serum creatinine and urine output. Both are included within regular criteria, however there are significant restrictions as far as early detection is concerned. Serum creatinine is a functional rather than direct indicator of renal tissue damage, and may not rise until there is a significant decrease in glomerular filtration. The age, muscle mass, nutritional status, fluid balance and medications also affect it. Urine output also can vary depending on hemodynamic status, fluid therapy and administration of diuretics. Therefore, traditional methods could underestimate early or sub clinical renal injury, and offer limited information regarding renal injury [2,3].

Such restrictions have spurred the quest to identify biomarkers that are specific to different facets of AKI such as tubular damage, cellular stress, changes in filtration, inflammation and susceptibility to injury. Emerging biomarkers are now being regarded as a complementary tool to serum creatinine which could enhance the timeliness and accuracy of the assessment of AKI. The Acute Disease Quality Initiative highlighted the importance of including biomarkers in the clinical assessment to help distinguish diagnosis, biological phenotype or to determine those at risk of

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needing more frequent monitoring and/or prevention measures [4]. This method has reinforced the concept of subclinical AKI, a state where there is molecular and/or structural damage, but not yet a traditional AKI diagnosis.

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most studied markers which is released quickly after tubular damage and has been measured in urine. It is hoped early rise is useful for the detection of AKI, before functional decline. For critically ill patients, urinary NGAL has proven to be useful in the early phase within the first hours of hospital admission to intensive care, and therefore may be used to detect renal injury early as a biochemical change is limited in those patients [5]. Additional biomarkers will give additional renal information. Proenkephalin has proven to be an indicator associated with glomerular filtration and could provide a responsive evaluation of acute kidney function changes in specific clinical situations [6].

Soluble urokinase plasminogen activator receptor is also of interest as it has been shown to have elevated circulating levels and be associated with a higher risk of AKI. Some biomarkers could be used for the diagnosis of established injury and biological vulnerability to renal dysfunction, and they could be employed for risk prediction, as well as diagnosis [7]. These markers might be useful to define susceptibility and facilitate earlier prevention in patients subjected to surgery, infection, nephrotoxins and hemodynamic instability.

Cell-cycle arrest markers, such as tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP7) are a key development in the research of biomarkers of AKI. The release of these proteins from stressed tubular epithelial cells can be elevated before any functional changes are detected. Both of their scores have been demonstrated to have added value in predicting AKI and the identification of those at higher risk of clinically significant renal dysfunction [8]. The results from critically ill populations also suggest that TIMP-2 and IGFBP7 may be valuable markers for the assessment of AKI risks, but their interpretation should take into account the timing, patient characteristics and clinical context [9].

Clinical utility of the biomarker-based risk stratification is known with high-risk surgical populations. Both urinary TIMP-2 and IGFBP7 have been found to be markers of a higher risk of postoperative AKI after cardiac surgery, and to be associated with strategies that can help prevent renal injury in these patients [10]. This is a concept that reflects the change in the way that AKI is managed, from the recognition of established AKI to the prevention of injury at an earlier time in the biological stress.

2. Pathophysiology and Clinical Spectrum of Acute Kidney Injury

Acute kidney injury (AKI) is a complex syndrome which results from the interplay of hemodynamic, inflammatory, metabolic, vascular and tubular changes. While the mechanisms of initiation vary, the biological pathway typically involves poor renal blood flow, endothelial dysfunction, oxidative stress, tubular injury, mitochondrial dysfunction and/or maladaptive repair. These processes can occur before there is an increase in serum creatinine, thus providing an early window in which there is some degree of cellular stress and damage, but apparently normal filtration. This dissociation adds to the increased desire for better biomarkers to refine the diagnosis and differentiate AKI phenotypes in a variety of contexts [11].

Many types of AKI are associated with hemodynamic instability. Reduced renal perfusion and a disturbance of autoregulation due to hypovolemia, hypotension, sepsis, cardiac dysfunction and perioperative blood loss. In the metabolically active tubular segments, there is a persistent oxygen imbalance leading to regional renal hypoxia. Then, ATP depletion, dysfunction of the mitochondria, loss of epithelial polarity and impaired transport contribute to tubular dysfunction. A secondary effect of injury to the epithelium is detachment of injured cells into the tubular lumen that can contribute to the obstruction and increase intratubular pressure. Inflammatory mediators exacerbate local tissue damage and endothelial activation and disturbed flow of microcirculation further contribute to hypothalazm. The functional decline is thus often a result of a complex interaction of the vascular, cellular and inflammatory disturbances.

Particular significance of tubular injury is due to their high metabolic needs and susceptibility to ischemic and toxic insults of the proximal tubule and the thick ascending limb. Liver-type fatty acid-binding protein (L-FABP) is synthesized primarily in the proximal tubular cells and is involved with oxidative stress and a change in fatty acid metabolism during tubular injury. Evidence from meta-analysis suggests that in the absence of significant functional loss, urinary L-FABP is a valuable tool for early detection of tubular stress, and therefore has useful accuracy for predicting AKI [12]. This demonstrates the general principle of structural biomarker being able to detect renal injury without any significant changes in serum creatinine.

Different settings may have different clinical manifestations of AKI. Relevant causes of renal injury in emergency surgery are blood loss, hemodynamic instability, systemic inflammation, exposure to nephrotoxic agents and fluid shifts. In a complex surgical setting, with multiple renal insults, urinary L-FABP has been shown to be an early marker of AKI after emergency laparotomy and has proved useful in such settings [13]. Cardiac surgery associated-AKA is also multi-factorial, with ischemia-reperfusion, cardiopulmonary bypass, hemolysis, oxidative stress, venous congestion, inflammatory activation and changes in renal perfusion all involved.

Cellular stress response is an important early phase of the evolution of AKI. There is some linkage between the inhibition of metalloproteinase by TIMP-2 and insulin-like growth factor by IGFBP-7 and their ability to arrest the cell cycle in tubules, thus delaying their entry into the cell cycle. They are increased in their urine concentrations prior to functional decline being apparent, and could be used to identify those patients who are at higher risk for clinically significant AKI. In cardiac surgery these markers have been compared to the risk assessment made by clinicians and have been found to bring additional valuable biologically relevant

information to the traditional assessment [14]. This early stress period may be a window to take action to protect the kidneys more than usual prior to irreversible injury.

Preventing established dysfunction through the recognition of biological stress has led to biomarker guided prevention. High risk categorisation based on urinary TIMP-2 and IGFBP-7 has been proposed as part of kidney disease: Improving Global Outcomes (KD:IGO) Kidney Care Bundles. This approach has been shown to be effective in certain high-risk groups with meta-analytic evidence to support this reduction in the incidence of AKI [15]. Early risk identification can then be correlated to preventive management by using biomarkers.

The results of AKI can vary from a quick recovery to ongoing severe kidney failure. The persistence is indicative of the continued tubular injury, inflammation, microvascular damage or failure to repair and is linked with increased risk of kidney replacement therapy, death, and chronic kidney disease. C-C motif chemokine ligand 14 has become a marker linked to prolonged severe AKI and standardised urinary chemistries have had use as a marker of renal dysfunction risk in prolonged patients [16]. These markers could help make the diagnosis of functional changes versus permanent damage.

3. Conventional Biomarkers in Acute Kidney Injury

Although the conventional biomarkers are important, they are still essential for diagnosis, staging and clinical monitoring of acute kidney injury (AKI). Serum creatinine and urine output are the basis of well-defined diagnostic criteria as they are inexpensive, routinely available and easily incorporated into clinical practice. Both, however, are mostly indicative of changes in renal function and not direct injury to the tissues. This is significant because functional deterioration can only be detected after structural and cellular damage has occurred. Thus, traditional biomarkers are still essential, but have to be used in the context of the overall biological and clinical profile of AKI.

Biochemical markers of kidney function are most commonly the serum creatinine. Its concentration depends on the ratio of endogenous production to renal elimination but is affected by other factors not related to renal function such as age, sex, muscle mass, nutritional status, fluid balance and exposure to medications. This may be delayed further by changes in creatinine production and volume of fluid in critically ill patients. This has led to an interest in cystatin C as an alternative functional marker. The production of Cystatin C is by nucleated cells and is freely filtered in the glomerulus, so that changes in filtration can occur with a relatively less muscle mass dependence. Cystatin C and measures of renal function derived from this protein have been shown to be associated with the development of AKI and mortality in patients with sepsis, which lend credence to its use as a functional assessment in critically ill patients [17]. All the conventional and emerging biomarkers across the spectrum of acute kidney injury are summarized in Table 1.

Table 1. Conventional and Emerging Biomarkers in Acute Kidney Injury

Biomarker	Biological Process Reflected	Stage of AKI Assessment	Primary Clinical Relevance
Serum creatinine	Decline in glomerular filtration	Established functional impairment	Diagnosis, staging, and serial monitoring of AKI
Urine output	Altered renal perfusion and tubular function	Early functional change	Bedside recognition of oliguria and evolving renal dysfunction
Cystatin C	Change in glomerular filtration	Early functional impairment	Earlier assessment of declining kidney function and risk
Blood urea nitrogen	Reduced nitrogenous waste clearance	Functional deterioration	Supportive evaluation of impaired renal excretory function
TIMP-2 × IGFBP7	Tubular cellular stress and cell-cycle arrest	Pre-injury/early stress phase	Identification of patients at increased risk of AKI development and progression
CCL14	Persistent tubular injury and inflammatory signaling	Persistent/severe AKI	Prediction of prolonged AKI and renal recovery trajectory

Urine output is another very important functional test and can change very quickly with alteration in renal perfusion and/or tubular function. The continuous monitoring is of great value in intensive care where oliguria may reflect progressive kidney failure, long before serum creatinine is elevated. However, low urine production does not necessarily mean there is kidney damage. In some cases where the patient has an established AKI, oliguria does not occur, and hypovolemia, transient hemodynamic changes, diuretic exposure, obstruction, and neurohormonal responses are all responsible in some cases. Therefore, urine output should be used in conjunction with biochemical markers with the hemodynamics and clinical response of the patient.

Other parameters such as blood urea nitrogen and routine urinalysis offer a background reference. The level of blood urea nitrogen can increase with decreasing renal clearance and is affected by dietary protein intake, catabolic state, gastrointestinal bleeding, corticosteroid use and volume status. The analysis of the urine may show patterns of renal injury, and the presence or absence of proteinuria, hematuria, cellular elements, and casts may help determine the pattern of renal injury, although the results do not always correlate with a specific pattern. The conventional laboratory assessment is thus most useful when used in conjunction with the other markers instead of alone.

In renal recovery, the drawbacks of conventional

markers are particularly noticeable. Functional improvement (improved urine output and falling creatinine) is generally used as evidence of recovery, but does not necessarily mean that tubular damage is completely resolved. The use of urinary biomarkers has been useful to predict successful acute dialysis withdrawal in critically ill patients, thus providing an additional biological information other than creatinine and urine output to assess recovery from acute dialysis [18]. The relationship between functional recovery and structural repair is important for clinical monitoring issues.

Meanwhile, the reverse is not necessarily true: a more sensitive diagnosis does not necessarily lead to better clinical results. Early injury biomarkers may detect biological abnormalities that only transiently exist or never lead to clinically relevant AKI. Too much use of markers that are very sensitive might then lead to an increase in diagnostic labelling without any benefit of improving management. However, the use of biomarker in conjunction with standard clinical and laboratory tests and clinical judgment is still critical to prevent overdiagnosis and unnecessary intervention [19].

As more evidence emerges, it is more evident that functional measures should be paired with biomarkers of persistent injury and/or of cellular stress. Stress biomarkers have been shown to have prognostic value for adverse outcomes of AKI beyond that of creatinine alone, and TIMP-2 and IGFBP7 have been shown to do so [20]. Urinary CCL14 has also been found to be a useful biomarker for renal recovery and distinguish patients with ongoing renal dysfunction from those who will recover [21]. Furthermore, the levels of TIMP2 and IGFBP7 in critically ill patients change with the course of illness, where the changes in these biomarkers reflect the changes in renal stress during illness [22].

4. Emerging Biomarkers for Early Detection of Acute Kidney Injury

Biomarkers are rapidly changing the way acute kidney injury (AKI) is assessed, and are detecting biological changes that happen before the conventional functional markers of AKI are abnormal. While serum creatinine is an essential tool in daily practice, it is not very sensitive in the initial stage of renal stress and structural damage due to its latency. Thus, modern biomarker studies are concentrated on markers of susceptibility, as well as glomerular filtration, tubular damage, inflammation and metabolic dysfunction that might be used alongside creatinine as a marker for diagnosis. Clinically important because the closer to the beginning, the earlier these measures can be implemented: prevention, avoiding nephrotoxin, hemodynamic optimization, and closer monitoring.

Soluble urokinase plasminogen activator receptor (suPAR) is a promising circulating marker of biological vulnerability and systemic inflammation for kidney injury. In multiple clinical settings, higher suPAR levels have been linked with increased risk for AKI, indicating that suPAR may serve as a predictor of patients who may be vulnerable to renal damage before clinical signs of functional injury become apparent. Increased levels of suPAR were consistently associated with subsequent AKI, and thus may be used for early risk prediction and patient stratification beyond renal failure alone, as shown by a systematic review and meta-analysis [23].

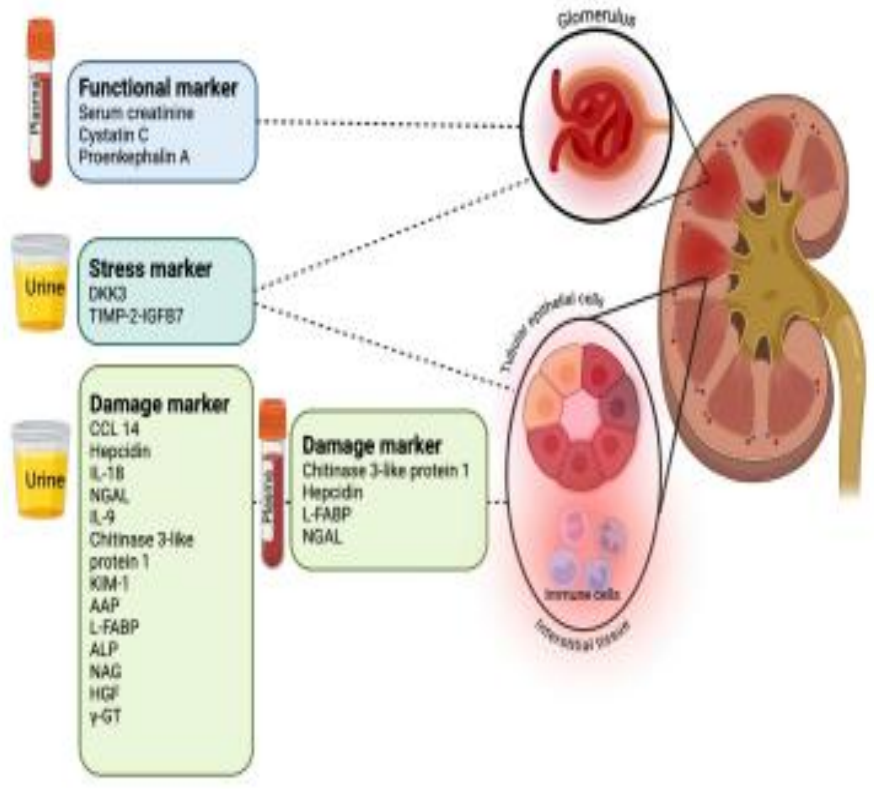

Figure 1. Functional, Stress, and Damage Biomarkers in Acute Kidney Injury
Source: Adapted by [24]

Another major step in early assessment of AKI is the development of proenkephalin. It is a circulating peptide and has been drawn to because it may react more quickly to alterations in renal clearance than does serum creatinine and is less influenced by muscle mass. Results of systematic review and meta-analysis suggest that elevated proenkephalin levels are significantly related to AKI, adding to its potential role in early detection, severity assessment and functional monitoring of acutely ill patients [25]. It is also important in the context of altered creatinine kinetics in critical illness, or fluid shifts, as it is biologically related to filtration.

In addition to protein biomarkers, metabolomics has also provided a wider avenue to identify AKI by blood and urine biochemical changes. Renal injury is characterized by alterations in cellular energetics, amino-acid metabolism, lipid handling, oxidative balance and mitochondrial function. Metabolomic approaches allow the simultaneous analysis of several small molecules, and thus can identify disease related signatures which cannot be identified with individual analytes. There is some clinical evidence that the selection of metabolites and metabolite patterns can contribute to the identification of early AKI, the classification of severity and information regarding recovery, but assay standardization and assay reproducibility are crucial to achieve widespread use.

Emerging biomarkers do not have limited use in diagnosis only. Their significance is growing throughout the entire spectrum of AKI, from determining renal recovery to decision making for kidney replacement therapy. Proenkephalin A 119-159 has been studied as a novel marker of recovering renal function in patients undergoing renal replacement therapy (RRT) in the critically ill setting. Multicenter data indicate that proenkephalin can provide valuable data to help determine readiness for dialysis freedom, particularly combined with urine output, trends in creatinine levels, and overall clinical stability. This goes beyond merely early detection to longitudinal evaluation of renal trajectory using biomarkers.

The increasing number of AKI markers could be understood in the context of precision medicine. AKI is a syndrome made up of different pathophysiological phenotypes that include tubular injury, inflammation, endothelial dysfunction, cellular stress, decreased filtration, and metabolic disruption. A combination of the markers reflecting these different processes may be able to better reflect renal injury than any single marker. Recent studies have highlighted the potential of using multimarker strategies to better differentiate between functional changes and structural injury, to label patients at risk for persistent AKI, and to enable more personalized clinical monitoring [28].

Interpretation of the biomarker, however, should remain closely connected with clinical context. Performance may be different depending on the etiology of AKI, when the sample was taken, patient co-morbidities, severity of the disease, and the method of the assay. A biomarker that is useful following cardiac surgery will not necessarily be useful following sepsis, nephrotoxic injury or emergency surgeries. In addition, serial measurement can be more informative than single testing as it represents a process from cell stress to cell injury, functional deterioration and recovery or chronicity.

5. Biomarkers for Risk Stratification and Clinical Decision-Making

The management of acute kidney injury (AKI) is greatly dependent on risk stratification, as the AKI syndrome occurs in diverse clinical contexts and can take on different courses. In some patients, the functional changes are temporary, in others renal dysfunction becomes permanent, oliguria occurs, and they become dialysis dependent or die. The traditional markers of renal function (serum creatinine and urine output) are important, but are frequently inadequate to give early clues to biological stress or the likely course of the disease. In addition to supporting patient care and clinical decision making by recognizing patients who are at higher risk for deterioration before it occurs, biomarkers can help tailor monitoring intensity and guide prompt prevention and/or treatment. The most important use of these is as a supportive diagnostic tool, not as a substitute for the accepted definitions [29]

Biomarkers are relevant beyond the intensive care unit (ICU) where acute kidney injury (AKI) can occur over several days. Hospitalized non-critically ill patients can have more than one risk factor, such as advanced age, chronic kidney disease, infection, surgery, exposure to nephrotoxic drugs and cardiovascular instability. The use of biomarkers early can identify patients who require more monitoring even if there is an acceptable serum creatinine. Biomarkers of tubular stress and injury could be useful in the early recognition of tubular involvement in non-critically ill populations and may be able to predict the risk of tubular involvement even before conventional criteria are met [30]. This allows for timely assessment of medication, fluid, hemodynamics and preventable renal insult.

The use of molecular signatures is expanding beyond protein biomarkers as an indicator of risk stratification. MicroRNAs are small non-coding RNAs which play a role in inflammation, apoptosis, fibrosis, oxidative stress, and tissue repair, as well as regulate gene expression. MicroRNA alterations in either the circulation or urine have been detected during AKI, and may precede detectable shifts in conventional functional markers. A systematic review and meta-analysis found a number of miRNAs that may be useful for predicting AKI, indicating the potential for molecular signatures to help better stratify patients by biological risk early in the course of diagnosis [31]. They are stable in biological fluids and are good candidates for multimarker panels. Table 2 will provide a summary of the clinical applications of the major classes of biomarkers in the risk stratification and decision making processes for AKI.

Table 2. Clinical Utility of Biomarker Classes for AKI Risk Stratification

Biomarker Class	Representative Markers	Biological/Risk Signal	Clinical Application
Functional markers	Serum creatinine, cystatin C	Decline in glomerular filtration	AKI staging, serial monitoring, and assessment of functional deterioration
Tubular stress markers	TIMP-2 × IGFBP7	Early tubular cell stress before overt dysfunction	Identification of high-risk patients and escalation of surveillance
Tubular injury markers	NGAL, KIM-1	Structural epithelial injury	Early recognition of renal injury and refinement of AKI severity
Molecular biomarkers	Circulating and urinary microRNAs	Gene-regulatory responses linked to inflammation, apoptosis, and repair	Biological phenotyping and early risk classification
Persistence/prognostic markers	CCL14	Sustained tubular injury and risk of persistent AKI	Prediction of oliguria, prolonged dysfunction, and kidney replacement therapy requirement
Integrated biomarker panels	Combined functional, stress, injury, and molecular markers	Multidimensional representation of AKI trajectory	Individualized risk stratification and clinically informed decision-making

Nevertheless, there is a need to be cautious of using microRNA signals to make clinical decisions. The level of a single microRNA can vary depending on the cause of the AKI, when the samples were taken, the type of assay to measure the microRNA, the presence of other disease, and the patient population. A systematic review of human studies of AKI also showed significant variation in the microRNAs studied and in the diagnostic performance reported so far, indicating the need for standardisation of measurement and external validation of the performance of these microRNAs for their wider use in clinical practice [32]. These results underscore another key concept in biomarker-based risk assessment: that of biological plausibility without consistency in performance is not enough unless the markers offer information that is clinically useful and that impacts patient care.

Urinary C-C motif chemokine ligand 14 (CCL14) has emerged as a promising biomarker for patients with established moderate-to-severe AKI and has proved to be particularly informative. It has been suggested that CCL14 is linked to inflammatory and tubular damage pathways and has been studied as a marker for ongoing renal function defects. Oliguria and higher requirements for dialysis have been correlated with higher urinary levels, which suggests that CCL14 could be used to differentiate patients that are likely to have a rapid clinical course from those at risk of a more severe clinical course [33]. This information could help with decisions about when and how to monitor, when nephrology is needed, fluid therapy, and preparation for kidney replacement therapy.

Decision making using biomarkers should thus be considered as an iterative process. Stress or injury markers can identify patients susceptible to stress or injury; molecular markers can enhance the ability to characterize a biological phenotype; and prognostic markers can predict progression or treatment needs. This has to be used in conjunction with baseline renal function, comorbidities, hemodynamic status, medications, urine output, and serial creatinine measurements. Additionally, biomarker assessment over time (serial assessment) might provide more information than a single measurement because the AKI process is dynamic and biological signals can shift over time before, during and after functional decline.

6. Prognostic Biomarkers for Acute Kidney Injury Outcomes

Prognostic evaluation has become a critical component of acute kidney injury (AKI) management because patients with similar degrees of initial renal dysfunction may follow different trajectories. Some recover rapidly after correction of the precipitating insult, whereas others develop persistent AKI, require kidney replacement therapy, progress to chronic kidney disease, or experience increased mortality. Serum creatinine and urine output remain essential for staging disease, but they provide limited information regarding the biological processes that determine persistence, repair, and long-term renal decline. Emerging biomarkers therefore offer an opportunity to move prognosis beyond functional assessment by identifying patients at increased risk of adverse short- and long-term outcomes.

C-C motif chemokine ligand 14 (CCL14) has emerged as one of the most promising biomarkers for predicting persistent severe AKI. Its principal value lies not simply in detecting renal injury, but in estimating whether established AKI is likely to continue. Persistent AKI is clinically important because longer duration of renal dysfunction is associated with greater risk of dialysis, hospitalization, incomplete recovery, and mortality. Expert consensus has highlighted the potential role of CCL14 testing in guiding clinical assessment, intensifying surveillance, and identifying patients who may require nephrology involvement or preparation for kidney replacement therapy [34].

The prognostic value of biomarkers is not confined to

patients with established severe AKI. Markers of tubular injury, cellular stress, inflammation, and altered filtration may provide early information about the likelihood of progression before indices fully reflect disease severity. Recent evidence indicates that early AKI biomarkers can contribute to prediction of worsening renal function, need for renal support, and recovery potential when interpreted alongside clinical risk factors and serial functional measurements [35]. This is relevant in critically ill and postoperative populations, where the clinical course can change rapidly and early identification of high-risk patients may influence monitoring and therapeutic intensity. The biomarker profiles associated with AKI progression, persistence, recovery, and long-term renal outcomes are illustrated in Figure 2.

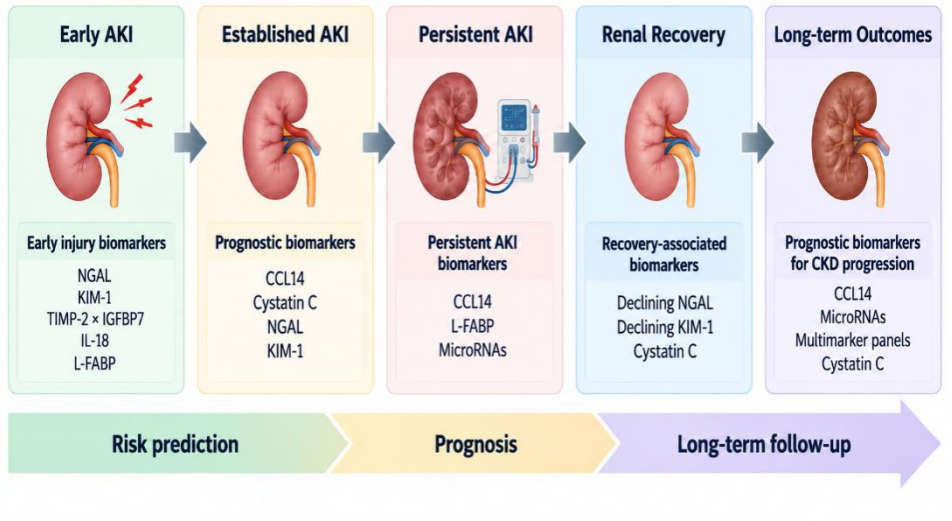

Figure 2. Biomarker Profiles for Predicting Progression and Recovery in Acute Kidney Injury

Persistent AKI has been identified as a phenotype rather than a continued manifestation of AKI. Failure to resolve injury, inflammation, microvascular disruption, and maladaptive repair may all play roles in delayed recovery of the tubular injury. Biomarkers reflecting these processes could, therefore, differentiate between transient AKI and disease that is more likely to be chronic. There were several biomarkers that exhibited significant predictive value for persistent AKI, but this depends on the patient population, timing of sampling, disease severity, and assay methodology [36]. These data justify a temporal strategy of prognosis that will involve successive changes in the interpretation of the biomarkers.

Important too is the long-term prognosis after apparent recovery. Cardiovascular complications, chronic kidney disease, loss of renal function and mortality are all potential complications of AKI that can occur in survivors. A return of serum creatinine towards baseline levels does not equate with a complete recovery of structure as there can still be ongoing inflammation, tubular damage, or fibrotic remodeling. Biomarker panels provide a broader strategy, combining signals from various pathways related to injury and repair. In AKI survivors, multibiomarker panels have shown promise for prediction of subsequent kidney disease progression, and could be used to target patients for more intensive follow-up after discharge and nephrology care [37].

Biomarkers are highly dependent for their prognostic performance on timing. Early measurements can identify those at risk of progression, while later measurements can better differentiate between persistence, recovery or progression to chronic dysfunction. A series of tests thus may be more informative than a single test, as it can reflect the direction and extent of biological change. Baseline kidney function, age, comorbid disease, etiology of AKI, severity of the illness, nephrotoxic exposure, and response to treatment should also be taken into account when interpreting.

7. Advances and Future Directions in AKI Biomarker Research

The research into the use of biomarkers in the diagnosis and prediction of acute kidney injury (AKI) is moving from ‘early detection’ to a ‘precision medicine’ approach that includes both diagnosis and prognosis, treatment guidance, and outcome assessment. This change has come about because it is now recognised

that AKI is not a single entity but a syndrome with associated tubular stress, inflammation, altered filtration, endothelial dysfunction, microcirculatory disturbance and tissue hypoxia. Going forward, the ability to identify individual markers becomes less important and more critical will be the ability to identify how complementary markers can be combined, timed and interpreted within the clinical context.

Widespread change towards multimarker assessment is a key development. Markers of various biological pathways might be able to give a more comprehensive picture of renal injury than any one marker. The MARKISIO study is a good example of this approach, which involves assessing a biomarker based on its capacity to predict intervention and/or clinically relevant outcomes and not only on diagnostic discrimination. This strategy is relevant as the more significant clinical usefulness of a biomarker might be in highlighting those patients who are likely to deteriorate, to require kidney replacement, to have ongoing function or to recover incompletely so that they can be monitored and managed more precisely [38].

Cell-cycle arrest biomarkers are still one of the most promising to assess early AKI. Tissues inhibitors of metalloproteinases (TIMP) 2 and insulin-like growth factor binding protein (IGFBP) 7 are indicators of tubular cellular stress and are elevated prior to the development of filtration loss. Their value in high risk situations is reinforced by evidence from systematic review and meta-analysis in adult intensive care patients [39]. Future research should explore more than just a threshold-based approach to interpretation and include serial testing, context-specific cut-offs, biomarker trajectory, and/or association with markers of structural injury, inflammation, or persistence.

In addition, physiological biomarkers are growing in scope for the assessment of AKI. Area of intrarenal oxygenation has become a possible urinary marker of intrarenal oxygenation, especially in medullary hypoxic areas. Disturbances in oxygen delivery and consumption can give rise to ischemic and hemodynamic injury to the kidney, which may lead to urinary monitoring of oxygen that can be a precocious marker of renal stress prior to the onset of traditional functional changes. It has potential application in the perioperative and critically ill population and measurement techniques, reference ranges, and interpretation of clinical use need to be standardized before its use is widespread [40].

Another future direction is the temporal profiling. A single value of a biomarker only reflects one point in the continuum of development associated with AKI. The serial measurements will provide an indication that the biological injury is resolving, stable or worsening. These pathways might help to distinguish transient hemodynamic fluctuation from permanent structural injury and help guide decisions regarding fluid management, exposure to nephrotoxic substances, nephrology consult, and initiation and termination of kidney replacement therapy.

In the future, the use of molecular and physiological signals is anticipated to be incorporated into the biomarker models, along with the routine clinical data. Several factors influence the risk for AKI and its outcomes, including baseline renal function, illness severity, urine output, hemodynamic variables, exposure to medications, and comorbidities. These along with known biomarkers can produce clinically meaningful, and accurate, risk profiles. Despite this, predictive models need to be transparent, repeatable and feasible, if they are to affect real-world decision making.

Analytical standardization, and clinical validation are essential for routine implementation. There are ongoing limitations in comparability between studies due to differences in sampling time, specimen type, assay platform, patient population and outcome definition. Multicenter studies are warranted to set firm thresholds, confirm the usefulness of combinations of biomarkers in different AKI phenotypes and show that the use of biomarkers for guiding care improves patient-centered outcomes. Other barriers to adoption will include cost, accessibility, turnaround time and integration into standard lab workflow.

8. Conclusion

Acute kidney injury is a significant clinical challenge, since the decline in measurable renal function may be after renal stress and damage have started. Serum creatinine and urine output continue to play a key role in the diagnosis and staging of AKI but neither reflects a comprehensive understanding of the earliest biological abnormalities or the entire spectrum of AKI. New biomarkers are thus changing the definition of assessment by capturing tubular damage, cellular stress, change in filtration, inflammation, metabolic changes, and the ability to recover. The markers such as NGAL, KIM-1, cystatin C, TIMP-2, IGFBP7, CCL14, suPAR, proenkephalin, metabolomic signatures and others have enhanced prospects of early detection, risk stratification, prediction of persistent injury and renal recovery. The most benefit that they offer is probably when they are used together instead of a single analyte. The use of functional, structural, stress and molecular markers in conjunction with serial clinical assessment may give a better picture of the trajectory of AKI, and guide more timely intervention. However, there is a long way to go before the broad clinical use of these assays, especially in terms of the universal acceptance of the assays' thresholds, as well as their sampling and validation in a range of populations and clinical settings. Further research is warranted in the use of multimarker approaches, longitudinal profiling, and evidence of improvement in meaningful outcomes for patients as a result of biomarker-based decision making. Advancement in the treatment of AKI will thus require more than only the identification of new AKI markers, but an understanding of the clinical implications of integrating current and new AKI markers into an actionable strategy. This change could help to better connect the dots from acute care to follow up. This integration may help identify patients at an earlier stage, help identify the type of patient more accurately, provide more individualized monitoring, and ultimately, lead to improved short- and long-term kidney outcomes.

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