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Update on Biomarkers of Acute Kidney Injury

Moving Closer to Clinical Impact?

Helmut Schiffl[1] and *Susanne M. Lang*[2]

1 Department of Internal Medicine IV, University of Munich, Munich, Germany
2 SRH Wald-Klinikum Gera, Department of Internal Medicine 2, Gera, Germany

Abstract

Acute kidney injury (AKI) represents a common disorder in hospitalized patients, and its incidence is rising at an alarming rate. Despite significant improvements in critical care and renal replacement therapies (RRT), the outcome of critically ill patients with AKI necessitating RRT remains unacceptably dismal. In current clinical practice, the diagnosis and severity classification of AKI is based on a rise in serum creatinine levels, which may occur 2–3 days after the initiating renal insult and delay potentially effective therapies that are limited to the early stage.

The emergence of numerous renal tubular damage-specific biomarkers offers an opportunity to diagnose AKI at an early timepoint, to facilitate differential diagnosis of structural and functional AKI, and to predict the outcome of established AKI. The purposes of this review are to summarize and to discuss the performance of these novel AKI biomarkers in various clinical settings.

The most promising AKI biomarkers include plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin (IL)-18, urinary liver-type fatty acid binding protein (L-FABP), urinary cystatin C, and urinary kidney injury molecule (KIM)-1. However, enthusiasm about their usefulness in the emergency department seems unwarranted at present. There is little doubt that urinary biomarkers of nephron damage may enable prospective diagnostic and prognostic stratification in the emergency department. However, comparison of the areas under the receiver-operating characteristic curves of these biomarkers with clinical and/or routine biochemical outcome parameters reveals that none of these biomarkers has a clear advantage beyond the traditional approach in clinical decision making in patients with AKI. The performance of various biomarkers for predicting AKI in patients with sepsis or with acute-on-chronic kidney disease is poor. The inability of biomarkers to improve classification of 'unclassifiable' (structural or functional) AKI, in which accurate differential diagnosis of pre-renal versus intrinsic renal AKI has the most value, illustrates another problem. Future research is necessary to clarify whether serial measurements of a specific biomarker or the use of a panel of biomarkers may be more useful in critically ill patients at risk of AKI.

Whether or not the use of AKI biomarkers revolutionizes critical care medicine by early diagnosis of severe AKI and individualizes the management of AKI patients remains to be shown. Currently, the place of biomarkers in this decision-making process is still uncertain. Indiscriminate use of various biomarkers may distract clinicians from adequate clinical evaluation, may result in worse instead of better patient outcomes, and may waste money. Future large randomized studies are necessary to demonstrate the association between biomarker levels and clinical outcomes, such as dialysis, clinical events, or death. It needs to be shown whether assignment to earlier treatment for AKI on the basis of generally accepted biomarker cut-off levels results in a reduction in mortality and an improvement in recovery of renal function.

1. Introduction

Acute kidney injury (AKI) [previously termed 'acute renal failure'] refers to a serious clinical disorder with an unpredictable outcome. It results from multiple causative factors and occurs in a variety of clinical settings, with clinical manifestations ranging from minimal elevations in serum creatinine levels to anuric renal failure.[1] AKI is common in hospitalized patients, particularly in critically ill patients. Worldwide trends suggest that the overall prevalence of AKI may be rising[2] as

aged patients with a high burden of coexisting diseases undergo extensive and aggressive diagnostic or therapeutic procedures. However, a large US national study found that the incidence of AKI in patients undergoing coronary angiography declined from 26.6% in 2000 to 19.7% in 2007. This may reflect increased clinician awareness, better risk stratification, or greater use of AKI prevention efforts during this time period.[3] Acute renal dysfunction occurs in 40–76% of intensive care unit (ICU) patients,[4,5] according to the RIFLE (Risk, Injury, Failure, sustained Loss, and End-stage kidney disease) criteria[1] (detailing serum creatinine changes or urine output reductions) used to diagnose and stage AKI.[6]

Risk factors and patient populations at risk have been identified, but the mechanisms underlying differences in the inter-individual susceptibility to AKI are unknown. Progression of AKI to a more severe RIFLE class (defined by further increases in the glomerular filtration rate [GFR] surrogate serum creatinine) occurs in a significant proportion of patients (31–56%) but not in all patients.[5,7] Approximately 4–6% of AKI patients[2] require renal replacement therapy (RRT).

Despite significant advances in intensive care medicine and in renal replacement techniques, the outcome of critically ill patients with AKI requiring RRT is poor. The in-hospital morbidity and mortality rates associated with AKI remain dismally high (40–60%) and have not appreciably improved during the last five decades.[2] Moreover, incomplete recovery of renal function from AKI causes excessive long-term morbidity and mortality, as well as development of chronic kidney disease or progression of pre-existing chronic renal failure to end-stage renal disease.[8] One potential reason for the poor outcome of ICU patients with severe AKI may be an unacceptable delay in the diagnosis of AKI and in the initiation of pharmacologic therapy.

2. Current Clinical Practice to Diagnose Acute Kidney Injury (AKI)

Most patients with AKI are asymptomatic, underlining the need for routine screening of patients at risk. The traditional diagnosis of AKI involves measurements of surrogate markers of the reduced GFR, such as a rise in serum creatinine levels and/or a reduction in urine output. However, measurement of serum creatinine levels has a number of limitations as a screening test in the early stages of AKI. First, serum creatinine levels reflect the renal filtering capacity, which is characterized by a large functional reserve. Second, the sensitivity of serum creatinine levels is diminished in certain patient sub-populations. Liver disease and low muscle mass, as seen in older patients, are known to decrease creatinine production, thus blunting a rise in serum creatinine levels. In addition, fluid overload secondary to aggressive volume resuscitation can result in a normal serum creatinine level although the GFR is in fact reduced. Moreover, even when serum creatinine levels increase in patients with AKI, a detectable rise does not occur until several hours (up to 2–3 days) after the precipitating renal insult. Finally, an increase in serum creatinine levels does not distinguish between pre-renal, intra-renal, and post-renal causes. Traditionally, abdominal ultrasound, urine chemistry, and urine microscopy have been used in the diagnosis of these causes of AKI. However, urine chemistry, such as the fractional excretion rate of sodium or urea, may be useful for differentiating pre-renal azotemia (functional change) from acute tubular necrosis (structural damage) only in selected patients. Volume status, fluid responsiveness, and diuretic use confound these tests. Urine microscopy using quantitative evaluation of urine sediment for renal tubular epithelial cells, renal tubular or erythrocyte casts, epithelial cell casts, and granular casts, as well as erythrocyte morphology, may differentiate pre-renal azotemia from acute tubular necrosis or acute glomerulonephritis.

3. Desirable Characteristics of Clinically Applicable AKI Biomarkers

Biomarkers are defined as parameters of structural, biochemical, physiologic, or genetic changes that indicate the presence, severity, or progress of a disease. As such, ideally a biomarker should be undetectable when there is no disease. Once the disease develops, the biomarker should become detectable. Biomarker expression should increase proportionally with disease severity, allowing quantification of disease severity and, ultimately, prognostic assessment and treatment of the disease.

1 The RIFLE criteria (Risk, Injury, Failure, sustained Loss, and End-stage kidney disease) are used to classify renal dysfunction according to the degree of impairment present:

- *Risk:* GFR decrease >25%, serum creatinine increased 1.5 times, or urine production of <0.5 mL/kg/h for 6 hours.
- *Injury:* GFR decrease >50%, doubling of creatinine, or urine production <0.5 mL/kg/h for 12 hours.
- *Failure:* GFR decrease >75%, tripling of creatinine or creatinine >355 μmol/L (with a rise of >44) [>4 mg/dL], or urine output below 0.3 mL/kg/h for 24 hours.
- *Loss:* persistent AKI or complete loss of kidney function for more than 4 weeks.
- *End-stage renal disease:* complete loss of kidney function for more than 3 months.

The characteristics of an ideal biomarker of AKI are as follows:[9,10]

- The biomarker assay should be non-invasive and easy to perform in a standard laboratory, using easily accessible samples such as blood or urine.
- The assay should be precise, accurate, and rapidly available to the clinician at a relatively low price.
- The biomarker should be highly sensitive to facilitate early detection, and generally accepted cut-off values should allow for risk stratification.
- The biomarker should be highly specific for AKI and enable identification of the causes of AKI.
- The biomarker should reflect the response to AKI interventions.
- The biomarker must provide additional information that is not surmised from clinical evaluation and standard laboratory measurements.

4. Selected Biomarkers of AKI

There is a steady rate at which new candidate markers of AKI are introduced into the literature. Therefore, any list of AKI biomarkers must be incomplete (table I). Generally speaking, the most promising biomarkers may be separated into different classes: (i) tubular cell enzymes released into the urine after cell injury; (ii) inflammatory mediators or cytokines released by kidney-specific cells or by infiltrating inflammatory cells; and (iii) low-molecular-weight proteins, which either are filtered freely in the glomeruli and not adequately reabsorbed or digested by injured tubular cells, or are released by injured tubular cells following AKI.[11]

Table I. Selected urinary biomarkers of acute kidney injury

Biomarker	Mechanism
Urinary tubular enzymes	
Glutathione-S-transferase	Released from lysosomes, brush-border, and cytoplasma of proximal tubular epithelial cells
γ-Glutamyltransferase	
N-acetyl-β-d-glucosaminidase	
Urinary low-molecular-weight proteins	
Urinary cystatin C	Filtered freely by the glomeruli, reabsorbed, non-secreted
Urinary inflammatory markers	
IL -1, -6, -8, and -18	Mediators of inflammation or injury
Matrix metalloproteinase-2	
Proximal tubular response	
NGAL	Upregulated in proximal tubular epithelial cells
KIM -1	
Cystatin C	
L-FABP	

IL = interleukin; **KIM** = kidney injury molecule; **L-FABP** = liver-type fatty acid binding protein; **NGAL** = neutrophil gelatinase-associated lipocalin.

5. Biomarker Exploration in Human AKI

A wealth of data from patient-oriented studies in various clinical settings has been compiled on the clinical utility of plasma or urinary biomarkers for early and sensitive detection and prognostic stratification of intrinsic AKI. While not trying to be exhaustive in this fast-moving field, we attempt to provide an overview of the utility of selected biomarkers to detect AKI, to differentiate causes of AKI, and to predict outcomes in patients differing in the severity of their underlying disease.

5.1 Prediction of Intrinsic AKI (Acute Tubular Necrosis due to Ischemia, Nephrotoxins, Sepsis)

Cardiac surgery, renal transplantation, or administration of contrast media have long been used to study AKI because of the ability to prospectively follow up patients before and after a well timed renal insult. A wealth of studies has implicated plasma neutrophil gelatinase-associated lipocalin (NGAL)[12,13] and urinary NGAL,[14,15] urinary cystatin C, urinary kidney injury molecule (KIM)-1, urinary interleukin (IL)-18,[16] glutathione-S-transferase,[17] and urinary liver-type fatty acid binding protein (L-FABP)[18] as early diagnostic biomarkers of AKI (at approximately 2 days). Currently, NGAL appears to be the most promising novel AKI biomarker – at least in homogeneous patient populations. However, the predictive ability of NGAL may be influenced by a number of patient characteristics, such as age and baseline renal function,[19] as well as the severity of AKI. A meta-analysis[20] of all published studies in patients with post-cardiac surgery AKI revealed an overall area under the receiver-operating characteristic curve (AUC-ROC) of 0.78 for prediction of AKI when urinary NGAL was measured within 6 hours of initiation of cardiopulmonary bypass. AKI was defined as a greater than 50% increase in the serum creatinine level. The same meta-analysis[20] reported an AUC-ROC of 0.89 for prediction of AKI when urinary NGAL was measured within 6 hours after contrast media administration. AKI was defined as an increase in the serum creatinine level of over 25%.

Urinary NGAL, KIM-1, L-FABP, IL-18, and cystatin C have been demonstrated to represent early biomarkers of nephron damage even in the heterogeneous group of critically ill patients with multiple comorbidities and with unknown

timing of AKI. However, urinary biomarkers detect or predict AKI in critically ill patients with a burden of comorbid disease with less specificity and sensitivity, as indicated by a much lower AUC value.[21]

A wealth of prospective studies has reported moderate or poor performance of urinary biomarkers in emergency department patients. Siew et al.[22,23] evaluated the urinary biomarkers IL-18 and NGAL in 451 critically ill patients and found that IL-18 did not reliably predict subsequent AKI within 24 hours (AUC-ROC 0.62). Furthermore, single measurements of NGAL exhibited only moderate predictive power for the development of AKI in these patients (AUC-ROC 0.71). It should be remembered that an AUC of 0.5 reflects the diagnostic accuracy of random allocation. The observation that the highest urinary IL-18 levels were observed in patients with sepsis at enrollment is of great interest. However, median IL-18 levels in patients with sepsis who developed AKI within 24 hours did not differ from IL-18 levels in those who did not. Comparable data have been reported by Endre et al.[24] in a prospective cohort of 529 ICU patients. On entry, none of the six biomarkers evaluated had an AUC above 0.7 in the diagnosis or prediction of AKI. The performance of these biomarkers was improved by stratification of baseline renal function and duration of renal injury, or both.

The TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in AKI) Consortium[25] conducted a prospective multi-center cohort study involving 311 children undergoing surgery for congenital cardiac lesions to evaluate whether early post-operative determinations of urinary IL-18 and urinary or plasma NGAL could identify which patients would develop AKI and other adverse outcomes. After multivariable adjustment, the highest quintiles of urinary IL-18 and NGAL were associated with higher odds of AKI. Elevated urinary IL-18 or NGAL levels were associated with longer hospital stay, longer ICU stay, and longer duration of mechanical ventilation. The accuracy of urine IL-18 or urinary NGAL for the diagnosis of severe AKI was moderate. Plasma NGAL did not predict AKI or poor outcomes in these patients.[25]

5.2 Prognostic Stratification of Critically Ill Patients, Using Urinary Biomarkers: Timing of Renal Replacement Therapy Initiation and Prediction of Outcome

A number of studies in pediatric patients have demonstrated the usefulness of early NGAL measurements for prediction of AKI. In children undergoing cardiac surgery, early post-operative plasma NGAL levels were strongly correlated with duration and severity of AKI, length of hospital stay, and mortality.[26] In a similar cohort of pediatric patients with post-cardiac surgery AKI, early urinary NGAL levels were highly correlated with duration and severity of AKI, length of hospital stay, dialysis requirement, and death.[27] Perianayagam et al.[28] measured serum cystatin C levels in 200 patients with AKI and found that serum cystatin C had an AUC of 0.65 for the composite endpoint of death and RRT. The performance of serum cystatin C, however, was inferior to a basic prediction model including the APACHE II (Acute Physiology and Chronic Health Evaluation II) score, liver disease, and mechanical ventilation (AUC 0.82). In a study by Liangos et al.[29] the AUC-ROC of KIM-1 for the prediction of RRT or death was 0.61 and comparable to those of serum creatinine and urine output. de Geus et al.[30] evaluated the ability of plasma and urinary NGAL to predict severe AKI in 632 consecutive adult critically ill patients. NGAL measured at ICU admission predicted the development of AKI for the RIFLE classes R and F (with AUC-ROC values of 0.77–0.92) but did not predict it more accurately than the serum level-derived estimation of the GFR.

Whether plasma cystatin C and urinary cystatin C are useful predictors of death or requirement for RRT is a subject of debate, because the number of patients needing RRT was relatively small in these cohorts. Nejat et al.[31] measured plasma creatinine and plasma cystatin C levels in 442 adults on ICU admission. Plasma cystatin C was moderately predictive of death or RRT (AUC-ROC 0.61) and performed similarly to plasma creatinine. Urinary IL-18 did not reliably predict AKI development in 451 ICU patients but did predict poor clinical outcomes (death or dialysis) within 28 days of development of AKI.[23]

The prospective observational study by Endre et al.[24] found that none of the five biomarkers studied had an AUC-ROC value above 0.7 for the diagnosis or prediction of AKI, but urinary NGAL, cystatin C, and IL-18 predicted death and need for RRT at 7 days (all with AUC-ROC values over 0.7).

A prospective observational study by Doi et al.,[32] including a cohort of 339 adult critically ill patients, revealed that all urinary biomarkers tested (L-FABP, NGAL, IL-18, N-acetyl-ß-D-glucosaminase) had moderate predictive values for the diagnosis of AKI (AUCs 0.62–0.75). Urinary L-FABP, NGAL, and IL-18 were able to predict 14-day mortality with higher AUC-ROC values than AKI diagnosis (L-FABP AUC-ROC 0.9, NGAL AUC-ROC 0.83, IL-18 AUC-ROC 0.83). The combination of urinary L-FABP and NGAL improved mortality prediction (AUC-ROC 0.93).

A multi-center prospective cohort study of 1635 unselected ICU patients, conducted by Nickolas et al.,[33] found good discriminatory acuity for urinary NGAL (AUC-ROC 0.81),

urinary KIM-1, and L-FABP (AUC-ROCs 0.72 and 0.70, respectively), and poor discriminatory acuity for urinary cystatin C and urinary IL-18 in the diagnosis of AKI (AUC-ROCs 0.65 and 0.64, respectively). Urinary NGAL and KIM-1 predicted a composite outcome of dialysis initiation or death during hospitalization, and both improved the net risk classification compared with conventional assessments.

5.3 Urinary Biomarkers for Differential Diagnosis of AKI

Identifying which patients have acute tubular necrosis and which have pre-renal dysfunction of the kidneys at the time of evaluation remains a clinical dilemma, which traditional fractional sodium excretion and urine microscopy cannot resolve.

Nejat et al.[34] stratified a total of 529 patients into four groups. The first group had no AKI, the second had AKI with recovery by 24 hours, the third had AKI with recovery by 48 hours, and the last group had a composite of AKI at greater than 48 hours or dialysis. Pre-renal AKI was identified in 61 AKI patients by recovery within 48 hours and by fractional sodium excretion of less than 1%. The median levels of urinary KIM-1, cystatin C, and IL-18 were significantly greater in pre-renal AKI compared with no AKI, while urinary NGAL and γ-glutamyl transpeptidase levels were not significantly increased. The median level of at least one biomarker was increased in all but three patients with pre-renal causes of AKI. The reason why some but not all biomarkers were increased remained obscure.

Nickolas et al.[33] performed a sub-analysis to assess the relationship between novel biomarker levels and the duration and severity of AKI. The entire cohort was categorized into three sub-groups, i.e. no AKI, transient AKI (defined as AKI that resolved by 72 hours), and sustained AKI (AKI that persisted for more than 72 hours). Urinary NGAL and cystatin C levels were significantly higher in patients with sustained AKI than in those with transient AKI. Urinary KIM-1, urinary L-FABP, and urinary IL-18 levels were no different in the groups with sustained and transient AKI.

Singer at al.[35] reported on the diagnostic value of urinary NGAL for the discrimination of intrinsic (acute tubular necrosis) and pre-renal AKI in 145 hospitalized patients. Using the current diagnostic standards, a history of precipitating renal insults, and response to volume resuscitation, they determined that 75 patients had intrinsic AKI, 32 had pre-renal AKI, and 38 patients could not be classified. Urinary NGAL levels effectively differentiated between intrinsic and pre-renal AKI (AUC-ROC 0.87). A urinary NGAL level over 104 μg/L indicated intrinsic AKI, whereas urinary NGAL levels less than 47 μg/L made intrinsic AKI unlikely. Patients experiencing a composite outcome (a step-up of RIFLE severity class, need for RRT, or death) had significantly higher median urinary NGAL levels. However, urinary NGAL was not helpful in those patients (38 out of 145) in whom no clear differential diagnosis could be made on the basis of current diagnostic standards, including fractional sodium excretion and microscopy.

Hall et al.[36] sought to determine the prognostic utility of novel biomarkers (urinary NGAL, KIM-1, IL-18) and traditional biomarkers (serum creatinine, fractional excretion of sodium or urea, urine microscopy) over clinical assessment alone in 249 ICU patients. AKI was considered as pre-renal (66%), acute tubular necrosis (20%), or other (14%). All urinary biomarker levels, fractional excretion rates of sodium and urea, and urine microscopy were statistically different between pre-renal and intrinsic AKI.

5.4 Detection of Sub-Clinical AKI by Use of Biomarkers

Haase et al.[37] analyzed pooled data from 2322 critically ill patients with predominantly cardio-renal syndromes from ten prospective observational studies of NGAL. Of the study patients, 1296 (55.8%) were NGAL negative and serum creatinine negative, 445 (19.2%) were NGAL positive and serum creatinine negative, 107 (4.65%) were NGAL negative and serum creatinine positive, and 474 (20.4%) were NGAL positive and serum creatinine positive. Accordingly, there were stepwise increases in the subsequent RRT initiation and in the median numbers of ICU days and in-hospital days. The authors concluded that in the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely sub-clinical AKI who have an increased risk of adverse outcomes. However, the concept and definition of AKI by biomarker positivity needs further prospective investigations.

5.5 Biomarkers Predict Progression of AKI After Cardiac Surgery

Being able to predict whether AKI will progress could improve monitoring and care, and could assist with enrollment into trials of AKI treatment. Using samples from the TRIBE-AKI study, Koyner et al.[38] evaluated whether kidney markers measured at the time of the first clinical diagnosis of early AKI after cardiac surgery could forecast AKI severity. The primary endpoint (progression of AKI defined by worsening AKIN [Acute Kidney Injury Network] stage) occurred in 45 patients (11.8%). The highest quintiles of all three biomarkers (urinary IL-18, urinary NGAL, and plasma NGAL) were associated with AKI progression, with plasma NGAL performing best.

6. Limitations of Urinary Biomarkers of AKI

One major problem that may hinder the successful testing of urinary biomarkers of AKI in large clinical cohorts is the lack of a reliable gold standard for the definition of AKI. The current practice of comparing increases in serum creatinine (which is well accepted to be a poor gold standard) with changes in urinary biomarkers has well known flaws. On the other hand, routine kidney biopsies in AKI are neither safe nor feasible, and there may be a dissociation between structural changes and functional decreases in acute tubular necrosis. The apparent diagnostic performance of a biomarker not only depends on its ability to detect renal injury but may also be a reflection of the imperfect gold standard itself.[39] Thus, evaluation of the performance of any biomarker is inherently flawed, and reported AUCs must be interpreted cautiously.

Generally, all urinary biomarkers of AKI may have several disadvantages, including the lack of samples available from patients with oligoanuria, and potential changes in urinary biomarker levels induced by hydration status, diuretic therapy, or primary polyuric AKI. The ideal method for quantifying urinary AKI biomarkers (i.e. the absolute level, or the biomarker level normalized to the urinary creatinine level or the biomarker excretion rate) is unknown. Ralib et al.[40] showed that the test characteristics of urinary biomarkers depended on the quantification method used in AKI. Estimated 24-hour excretion rates of different biomarkers (including cystatin C, NGAL, KIM-1, and IL-18) in 528 critically ill patients were associated with AKI severity, and those of NGAL and cystatin C were associated with survival. The commonly employed correction for urinary dilution is to express urinary biomarker levels adjusted for the urinary creatinine level. However, this correction may be inaccurate in the situation of AKI because creatinine production may be altered in some forms of AKI, and both plasma and urinary creatinine levels are significantly altered in the early phases of AKI.[41]

The performance of AKI biomarkers is effectively modified by the methods of determination used and the characteristics of the patient population studied. The majority of NGAL results described in the literature have been obtained by using research-based ELISA assays, which are not practical in the clinical setting. The global deployment of standardized clinical laboratory platforms is highly promising for more uniform interpretation of the results. In fact, different cut-off levels for urinary NGAL have been described (more than 10 μg, more than 60 μg, and more than 100 μg) to identify patients who will potentially develop AKI. The age of the patients, method of measurement (research-based ELISA versus the routine laboratory platform), urinary tract infections, comorbidity (malignancy, pancreatitis, chronic obstructive pulmonary disease, endometrial hyperplasia, and associated increases in plasma NGAL) and chronic kidney diseases appear to be modifiers of the predictive performance of NGAL.[42] However, it should be noted that these increases in plasma NGAL in coexisting diseases are generally much lesser than those typically seen in AKI. The levels of urine NGAL in chronic kidney disease are also significantly blunted compared with those typically measured in AKI.[43] Cullen et al.[44] established a 95th percentile cut-off level for urinary NGAL (107 μg/L) in a reference population. There were significant gender-related differences in urinary NGAL, with women having higher levels. There were also age-related differences in urinary NGAL levels between the 40- to 59-year and 60- to 88-year age categories. Of interest, the authors found significantly higher levels of NGAL in patients with leukocyturia. Plasma cystatin C levels are altered in patients with systemic inflammation, malignancy, thyroid disorders, or glucocorticoid deficiency, and in smokers.[45]

Different biomarkers reach peak levels at different timepoints after post-surgical AKI.[46] Urinary NGAL was found to be significantly increased in pediatric patients with post-surgical AKI at 2 hours after cardiopulmonary bypass initiation, IL-18 and L-FABP were increased at 6 hours, and KIM-1 was increased at 12 hours, but the complete time course of urinary levels for each urinary biomarker in AKI due to different or multiple causes is not known. Additional urine collections were needed beyond the first 24 hours after surgery to validate the role of some urinary biomarkers for the early detection of late post-operative AKI.[47] Thus, how to combine multiple biomarkers for clinical use remains a challenge.

Currently, it appears unclear whether measurement of a single biomarker performs better in prognostic stratification than the clinical expertise of the treating nephrologists/intensivists or conventional biomarkers such as serum creatinine or urinary output. Although Koyner et al.[15] were unable to predict AKI by using urinary NGAL or cystatin C, they found a very high predictive power for the need for RRT. One wonders, however, whether clinical evaluation could not predict this outcome equally well. Moreover, extracorporeal perfusion time or clinical appraisal predicted AKI in patients after coronary bypass surgery with the same performance as plasma IL-18.[29]

Currently, there are doubts about the clinical usefulness of NGAL in patients with sepsis, one of the leading causes of intrinsic AKI in ICU patients. Plasma NGAL or urinary NGAL levels can be significantly elevated in patients who have sepsis without AKI. Of great interest, elevated plasma NGAL levels predicted severe sepsis in patients admitted to ICU for suspected infection.[48]

7. Limitations of the Reported Investigations

The majority of studies reported were from single centers that enrolled small numbers of subjects. However, the number of multi-center investigations is rapidly increasing. Unfortunately, most studies reported to date did not include patients with pre-existing chronic kidney disease. This is problematic, as it excludes not only a significant proportion of hospitalized patients (approximately 30%) but also a risk group who frequently develop acute-on-chronic kidney injury. There are studies demonstrating that the utility of urinary markers may be affected by pre-existing chronic kidney disease.[15,19]

Only a few studies have investigated biomarkers for AKI severity, morbidity, and mortality, and the definition of AKI varied widely. In most studies, it was based on elevations in serum creatinine levels, raising doubts about its validity.

A few studies examining urinary NGAL, cystatin C, or KIM-1, among others, have suggested that these biomarkers have the potential to distinguish patients with severe AKI requiring RRT. However, currently available data are not sufficient to conclude that biomarkers should be used for the clinical decision to commence RRT.[45]

Using changes in serum creatinine may confound the results of biomarker assays because of lack of accuracy due to either false positives (true tubular injury, but no significant change in serum creatinine) or false negatives (absence of tubular injury, but elevations in serum creatinine due to pre-renal causes of AKI or any of a number of confounding variables that haunt measurement of biomarkers). It will be crucial for future studies to understand the clinical outcomes of patients who are prone to sub-clinical AKI and are biomarker positive but serum creatinine negative. Undoubtedly, there is a need for investigations showing an agreement of histopathologic findings with biomarker positivity, since this will determine whether a biomarker is overtly sensitive.[49]

8. Conclusions

Whether or not novel biomarkers have the potential to revolutionize renal and critical care of AKI patients by adding substantially to the current diagnostic systems for AKI or to successful interventions (if used earlier in the course of AKI) remains unclear. On the contrary, the use of these biomarkers may distract clinicians from adequate clinical evaluation of patients and carries the risk of worse instead of better patient care and outcomes.

Multi-biomarker panels will likely aid the diagnosis of various types of AKI, but one must recognize the different inherent performance characteristics of the individual biomarker and the simple fact that AKI is a heterogonous syndrome. The biomarker profile of cardiac surgery-induced AKI may be different from that of septic AKI, which will be different from those of causes such as toxin-induced or obstructive AKI.

The use of such AKI biomarkers is a potentially valuable clinical strategy that may allow clinicians to aggressively and appropriately treat and triage those patients with impending severe AKI. However, it is unclear whether early prediction of AKI and pharmacologic interventions will improve care and reduce adverse events of AKI in clinical practice.[50] Whether or not earlier initiation of RRT for AKI reduces overall mortality and development of chronic kidney disease due to AKI, as suggested by observational studies, remains to be shown by adequately powered randomized prospective investigations. Moreover, a considerable proportion of AKI patients starting RRT at early RIFLE class stages (R, I) are likely to spontaneously recover renal function before significant sequelae of AKI, such as fluid overload or azotemia, develop. Thus, the potential benefits of RRT may not exceed the potential risks of extracorporeal blood purification.

The currently published investigations consistently show that urinary AKI biomarkers are not the panacea that will correctly identify 100% of all AKI patients before the current standard serum creatinine measurement does the same.

Documentation of the presence or increased levels of urinary biomarkers may, in a significant number of patients, detect mild or transient renal dysfunction that is presently undetected by traditional markers of AKI. The clinical relevance of this requires further evaluation of the sensitivity of the biomarkers.

It is unclear whether biomarkers should be measured in all patients in the ICU or whether sub-populations at risk should be selected.

There is an urgent need for further data. It is vital that additional large future studies clearly demonstrate the association between biomarkers and hard clinical outcomes, independent of serum creatinine levels, and that randomization to renoprotective treatment or early initiation of RRT on the basis of high biomarker levels results in a significant improvement in clinical outcomes compared with traditional diagnosis of AKI.

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Correspondence: Prof. Dr. *Helmut Schiffl*, Medizinische Klinik und Poliklinik IV-Campus Innenstadt, Universität München, Ziemssenstr. 1, D-80336 München, Germany.
E-mail: h-schiffl@t-online.de