R E V I E W

Biomarkers for early detection of acute kidney injury

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Abstract: It is very difficult to make an early diagnosis of acute kidney injury (AKI) using serum creatinine, which is the standard metric tool for the detection of renal injury. The absence of sensitive AKI biomarkers has impaired progress in the nephrology field and had a detrimental effect on the design and outcome of AKI clinical trials. Recently, several proteins have shown potential in the early detection of AKI, including neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and interleukin-18. This review discusses the current status of three AKI biomarkers as a potential diagnostic tool for the early detection of AKI. The focus is limited to prospective human studies from January 2005 to December 2011. The review compares the clinical conditions for which the AKI biomarkers have the greatest potential utility for the early detection of AKI. It also demonstrates the barriers to the successful use of AKI biomarkers in clinical practice, as well as the future trials that will be needed to validate their use. Despite the early promise of biomarkers such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and interleukin-18 for the early detection of AKI, none of these biomarkers has demonstrated a clear benefit in detecting various types of AKI in daily clinical practice. Indeed, the majority of published clinical studies of known AKI biomarkers so far are small and insufficient to support clinical studies of AKI biomarkers as an effective early AKI diagnostic test in humans.

Keywords: acute kidney injury, biomarker, early detection

Introduction
Acute kidney injury

Acute kidney injury (AKI) is a heterogeneous entity associated with various clinical presentations, treatments, and procedures. It represents a clinical situation that can vary from subclinical renal injury, in which serum creatinine (SCr) changes minimally, to severe oliguric renal injury associated with tubular necrosis with failure of function. AKI is often found in the setting of multiple organ failures and sepsis, and is an important cause of morbidity and mortality in hospitalized patients. The main cause of hospital-acquired AKI is one or more events of ischemic insult and nephrotoxic injury to kidneys. The incidence of hospital-acquired AKI varies from 5% in patients with normal renal function to 25% in intensive care unit (ICU) patients.[1,2] Mortality rates of patients with postoperative AKI range from 50% to 70% among ICU patients who require renal replacement therapy (RRT).[3,4] For the last 40 years, the mortality rate of patients with severe AKI requiring RRT in the ICU has not decreased significantly despite advances in supportive care, including continuous RRT.

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77

Defining AKI and the limitations of current AKI criteria

There are more than 30 definitions for the diagnosis of AKI in published studies, most based on SCr values. The lack of a standard definition of AKI has had a detrimental effect on clinical trials in the diagnosis of AKI. Recently, two new definitions of AKI have been developed as the uniform standard for the diagnosis and classification of AKI: RIFLE (risk, injury, failure, loss, and end-stage renal disease) and AKIN (acute kidney injury network).[5,6] It is, however, a challenge to detect AKI in a timely fashion with current RIFLE and AKIN criteria since these definitions are entirely based on SCr increases or decreases in urine output. SCr is insensitive for the early detection of AKI because the change in SCr does not discriminate the time and type of renal insult or the site and extent of glomerular or tubular injury.[7–9] Therefore, current AKI criteria do not allow for the early detection of AKI in a timely fashion so that intervention can be initiated. There is currently no standard definition for AKI that is not based on a change in SCr.

The lack of reliable biomarkers for the early detection of injury leads to delays in the introduction of treatment until well into the course of the renal injury. Previous animal studies clearly demonstrate that treatment must begin well before the rise of SCr and very early after the insult.[10–14] Therefore, it is not surprising that many potential therapeutic agents show little success in human studies.[15–19] There are currently no effective therapies available for the prevention and/or treatment of AKI. Dialysis remains the only FDA-approved treatment option for established AKI.

New biomarkers under evaluation

It has been postulated that introducing therapy early in the disease process would reduce the mortality rate associated with AKI. Several proteins and biochemical markers emerged as sensitive and specific biomarkers capable of the early detection of acute tubular injury through the application of functional genomics and proteomics to human and animal AKI models, and have proven to be promising biomarkers as indicators of renal injury in recent human studies.[20–23] These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), cystatin C, and L-fatty acid binding protein.

Previous cross-sectional studies clearly established that new AKI biomarkers can differentiate patients with established AKI from patients without AKI. However, a cross-sectional study gives no indication of whether new AKI biomarkers are useful for the early detection and prognosis of AKI. Current AKI biomarker studies are past cross-sectional measurements unrelated to a clinically or biochemically defined end point. The inherent benefit of new AKI biomarkers is for making an early diagnosis of AKI that correlates with future declines in renal function as detected by changes in SCr, not when SCr is already grossly elevated. The successful prediction of AKI at an early stage may allow potential therapies to be evaluated earlier, at a stage when they are more likely to be successful.

The author focuses this review on the current status of NGAL, KIM-1, and IL-18 as potential diagnostic tools for the early detection of AKI in prospective human clinical studies. A comprehensive review on promising AKI biomarkers is beyond the scope of this paper and can be found elsewhere.[24,25]

Methods of quantitation and stability of urinary proteins

Several methods have been used for the measurement of AKI biomarkers in published studies. Current quantification methods include enzyme-linked immunosorbent assay, microsphere-based Luminex assay, and nephelometry. In addition, the Triage NGAL device (Biostite Incorporated, San Diego, CA), ARCHITECT analyzer (Abbott Diagnostics, Abbott Park, IL), and KIM-1 RenaSticks (Argutus Medical, Dublin, Ireland) have been developed as point-of-care tests (POCs) for NGAL and KIM-1, respectively.[26–28]

The optimal methods for collecting, handling, and storing biological samples also need to be established as a necessary first step before testing the clinical utility of laboratory tests. Failure to do so may result in erroneous conclusions based on an extrinsic factor such as a compound's poor stability at room temperature and prolonged storage with repeated freeze-and-thaw cycles. Urinary NGAL (uNGAL) and KIM-1 (uKIM-1) proteins did not degrade significantly for up to 24 hours at 4°C and at room temperature, and for up to 1 year in prolonged storage at −80°C with repeated freeze-and-thaw cycles.[29] Unpublished data indicate that urinary IL-18 (uIL-18) was stable for at least 4 hours at room temperature and for 24 hours at 4°C (Table 1). The addition of a protease inhibitor was not necessary to prevent the degradation of the uNGAL, uKIM-1, and uIL-18 proteins. Further studies are necessary to determine the stability of the various other AKI biomarkers in routine clinical storage conditions, including a number of freeze-thaw cycles. These findings are

Table 1 Stability of urinary biomarkers

Collection and processing	Mean percentage difference when compared to immediate storage at −80°C		
	KIM-1 (n = 12)	NGAL (n = 12)	IL-18 (n = 8)
At RM for 4 hrs	−2.1	−3.9	−7.1
At RM for 24 hrs	−7.2	−11.9	−80.2
At 4°C for 4 hrs	−1.3	+3.0	−0.7
At 4°C for 24 hrs	−3.3	−2.5	−1.3
PI vs no PI	0.5	−0.8	+7.3

Note: Immediate storage at −80°C, place urine samples at −80°C within first 20 minutes after collection.
Abbreviations: IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; PI, protease inhibitor; RM, room temperature.

critical to continuing validation studies of potential tandem AKI biomarkers.

Utility of AKI biomarkers for the early detection of AKI

The following section discusses in detail the potential role of NGAL, KIM-1, and IL-18 as diagnostic tools for the early detection of AKI in prospective human clinical studies.

Neutrophil gelatinase-associated lipocalin

NGAL is a member of the lipocalin superfamily. Lipocalin family members are thought to transport a variety of ligands within a β-barreled calyx.[30] The human form was originally identified as a 25-kDa protein covalently bound to gelatinase from human neutrophils and found to be highly expressed in the early postischemic mouse and rat kidney.[31] The expression of the NGAL protein is detected predominantly in proliferating cell nuclear antigen-positive proximal tubule cells. The major ligands for NGAL are siderophores, which are small, iron-binding molecules. Siderophores produced by eukaryotes participate in NGAL-mediated iron shuttling that is important to various cellular responses, including proliferation and differentiation.[32]

NGAL has been implicated as an early predictive biomarker of ischemic AKI in several small, prospective single-center studies in children undergoing open-heart surgery (Table 2).[26,27,33,34] AKI was defined as a 50% increase in SCr occurring 1–3 days after surgery. uNGAL and plasma NGAL (pNGAL) were increased within 2–6 hours of cardiopulmonary bypass (CPB) and preceded an increase in SCr by 1–3 days in children who subsequently developed AKI. The area under the receiver operating characteristic curve (AUC-ROC) was >0.90 for the 2–6 hours following CPB. These studies demonstrated great NGAL performance in the

early detection of AKI. However, patients with chronic kidney disease (CKD), diabetes mellitus, and peripheral vascular disease, which are common co-morbidities in adult patients undergoing cardiac surgery, were excluded. Most of the AKI suffered was likely a result of mild to moderate tubular injury. Only a few patients required dialysis.

However, there is a large discrepancy in the performance of NGAL as an early AKI biomarker between adult and pediatric AKI patients (Table 2). Parikh et al[35,36] conducted a multicenter prospective cohort study of 1219 adults and 311 children undergoing cardiac surgery. The AUC-ROC for the prediction of AKI was rather disappointing for NGAL. The clinical prediction model for AKI had an AUC-ROC of 0.69, while uNGAL and pNGAL have AUC-ROC values of 0.67 and 0.70, respectively, for adult AKI patients. Meanwhile, uNGAL and pNGAL have AUC-ROC values of 0.71 and 0.56, respectively, for pediatric AKI patients. NGAL performed poorly for the early detection of AKI after surgery in this study. This finding is, however, similar to existing published studies among adult patients. In a single-center prospective study of 426 adult patients, uNGAL levels were increased within 1 hour of CPB and found to have AUC-ROC values of 0.60 at 3 hours and 0.61 at 18 hours after CPB.[37] Koyner et al[38] also reported that uNGAL has an AUC-ROC value of 0.61–0.70 at various time points after cardiac surgery in adult patients. Meanwhile, Haase-Fielitz et al reported that pNGAL had an AUC-ROC value of 0.80–0.87 for the prediction of AKI within 24 hours of cardiac surgery in adult patients.[39] The reasons for this discrepancy are not completely clear.

NGAL also demonstrated as a predictor marker for AKI in both pediatric and adult critically ill patients (Table 2). NGAL was able to predict the development of AKI about 1–2 days prior to the increase in SCr.[40–44] Its AUC-ROC values were 0.68–0.78 and 0.71–0.92 among pediatric and adult critically ill patients, respectively. However, most of these studies were small and/or single-center studies. NGAL was also associated with a predictor of contrast-induced nephropathy (CIN) following IV contrast dye exposure in several small prospective studies of children and adults undergoing cardiac catheterization (Table 2). However, these studies were very limited because there were few cases of CIN without information on the severity and outcome of AKI.[45–47] Furthermore, there was no direct comparison of SCr with AKI biomarkers for the detection of CIN.

NGAL appears to be a more sensitive and specific AKI biomarker in pediatric patients. It is possible that a lack of standardization for the measurement of NGAL

Table 2 Prospective studies of NGAL for early detection of AKI

Clinical study	Study population	Type of study	Major findings	Limitations
Cardiac surgery				
Mishra et al[33]	Pediatric cardiac surgery patients (n = 71)	Prospective study (uNGAL and pNGAL)	AUC-ROC of 0.99 at 2 hr after surgery	Single center study No patients with severe AKI
Dent et al[26]	Pediatric cardiac surgery patients (n = 120)	Prospective study (pNGAL)	AUC-ROC of 0.96 at 2 hr after surgery	Single center study
Bennett et al[27]	Pediatric cardiac surgery patients (n = 196)	Prospective study (uNGAL)	AUC-ROC of 0.95 at 2 hr after surgery	Single center study
Wagener et al[37]	Adult cardiac surgery patients (n = 426)	Prospective study (uNGAL)	AUC-ROC of 0.60, 0.61 and 0.58 at 3 hr, 18 hr, 24 hr after surgery, respectively	Single center study
Koyner et al[38]	Adult cardiac surgery patients (n = 72)	Prospective study (uNGAL, pNGAL, and others)	AUC-ROC of 0.61–0.70 and 0.45–0.54 at first 6 hr after surgery for uNGAL and pNGAL, respectively	Single center study
Haase-Fielitz et al[39]	Adult cardiac surgery patients (n = 100)	Prospective study (pNGAL and others)	AUC-ROC of 0.8–0.89 for NGAL on arrival at ICU	Single center study
Krawczeski et al[34]	Pediatric cardiac surgery patients (n = 374)	Prospective study (uNGAL and pNGAL)	AUC-ROC of 0.95 at 2 hr after surgery	Single center study
Parikh et al[35,36]	Adult (n = 1219) and pediatric (n = 311) cardiac surgery patients	Prospective multi-centered study (uNGAL, pNGAL, and others)	AUC-ROC of 0.67 and 0.70 (adult) and 0.71 and 0.56 (children) for uNGAL and pNGAL, respectively	
Critical care				
Zappitelli et al[40]	Pediatric critically ill patients (n = 140)	Prospective study (uNGAL)	AUC-ROC of 0.78 for predicting AKI development within next 48 hr	Single center study and small sample size
Wheeler et al[41]	Pediatric critically ill patients with septic shock (n = 168)	Prospective study from 15 PICUs (pNGAL)	AUC-ROC of 0.68 for predicting AKI development	Small sample size Control group was from healthy children
Siew et al[42]	Adult critically ill patients (n = 450)	Prospective study (uNGAL)	AUC-ROC of 0.71 and 0.64 for predicting AKI development within next 24–48 hr	Clinical model has better performance for AKI prediction
Constantin et al[43]	Adult critically ill patients (n = 88)	Prospective study (pNGAL)	AUC-ROC of 0.92 for predicting AKI development at ICU admission	32 out of 52 AKI patients already had elevated SCr at the time of ICU admission
Cruz et al[44]	Adult critically ill patients (n = 301)	Prospective study (pNGAL)	AUC-ROC of 0.78 for predicting AKI development within next 48 hr	Single center study
Contrast induced nephropathy				
Bachorzewska-Gajewska et al[45]	Adult patients for cardiac catheterization (n = 35)	Prospective (uNGAL and pNGAL)	uNGAL and pNGAL were elevated 2–4 hr and 4–12 hr after IV contrast exposure	Single center study No episode of CIN
Hirsch et al[46]	Pediatric patients for cardiac catheterization (n = 91)	Prospective (uNGAL)	uNGAL and pNGAL were elevated 2 hr after IV contrast exposure, while SCr was elevated in 6–24 hr after IV contrast exposure	Single center study No information on severity and outcome of CIN
Malyszko et al[47]	Adult patients for cardiac catheterization (n = 140)	Prospective (uNGAL, pNGAL, and others)	uNGAL and pNGAL were elevated within 4 hr after IV contrast exposure	Single center study No informaiton on severity and outcome of CIN

Abbreviations: AKI, acute kidney injury; AUC-ROC, area under the receiver operating characteristic curve; CIN, contrast-induced nephropathy; NGAL, neutrophil gelatinase-associated lipocalin; pNGAL, plasma neutrophil gelatinase-associated lipocalin; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

and optimal methods for collecting, handling, and storing biological samples may contribute to the large discrepancy between studies. In addition, the ideal method for quantifying urinary AKI biomarkers has not yet been established. Normalization of urinary biomarker concentration to urine creatinine concentration can be inaccurate because of non-steady states of creatinine balance in patients with AKI. Finally, the majority of published studies were from single centers that enrolled small numbers of patients and did not include patients with CKD. Such population studies are not representative of the global group of patients with AKI. Larger multi-center studies that are sufficiently powered are necessary to validate the role of biomarkers for the early detection of AKI.

Kidney injury molecule-1

Human KIM-1 is a type 1 transmembrane glycoprotein containing a novel 6-cysteine immunoglobulin-like domain and a threonine-/serine- and proline-rich domain characteristic of mucin-like O-glycosylated proteins.[48] KIM-1 is also known as the hepatitis A virus cellular receptor 1 and T-cell immunoglobulin- and mucin-domain-containing molecule 1.[49,50] The KIM-1 family consists of eight members in mice, six in rats, and three in humans.[51,52] The KIM-1 protein is not detectable in normal kidney tissue or urine but is expressed at high levels in dedifferentiated proximal tubule epithelial cells in human and rodent kidneys after ischemic or toxic injury, and in RCC.[48,53–56]

KIM-1 has been implicated as a urinary biomarker for postoperative AKI in pediatric and adult patients (Table 3).[29,57,58] AKI was defined as a 50% increase in SCr occurring 1–3 days after surgery. uKIM-1 was increased within 2–12 hours after surgery and preceded an increase in SCr by 1–2 days in patients who subsequently developed AKI. The AUC-ROC values ranged from 0.78 to 0.83 at various time points after surgery.

The heterogeneity of AKI suggests that more than one AKI marker may be necessary to obtain sufficient sensitivity and specificity for AKI screening. Han et al[29] demonstrated that combining multiple urinary AKI biomarkers enhanced the sensitivity of the early detection of postoperative AKI compared to individual biomarkers. Different biomarkers reached peak levels at different time points after operation. How to combine multiple biomarkers at various time points for clinical use remains a challenge. Furthermore, additional urine collections are needed beyond the first 24 hours after surgery to study the temporal expression patterns of AKI biomarkers for late postoperative AKI.

In a small prospective study, uKIM-1 was associated as a predictor of CIN. Malyszko et al[47] evaluated the utility of urinary biomarkers for the detection of CIN in 140 patients without CKD after cardiac catheterization. Seventeen patients developed CIN, which was defined as an increase in SCr $\geq$ 25% of baseline within 48 hours of cardiac catheterization. uKIM-1 levels were increased at 24 and 48 hours post-catheterization for the CIN group, but without statistical significance. However, there is no information on the severity and outcome of CIN. Direct comparison of SCr with AKI biomarkers for the detection of AKI was not done. Overall, there have been no larger prospective multi-center studies to validate the temporal

Table 3 Prospective studies of KIM-1 for early detection of AKI

Clinical study	Study population	Type of study	Major findings	Limitations
Cardiac surgery				
Han et al[57]	Pediatric cardiac surgery patients (n = 40)	Case control study (uKIM-1 and others)	AUC-ROC of 0.57, 0.83 and 0.78 at 2 hr, 12 hr and 24 hr, respectively	Single center study and small sample size. No patients with severe AKI
Han et al[29]	Adult cardiac surgery patients (n = 90)	Prospective study (uKIM-1 and others)	AUC-ROC of 0.75 and 0.78 at immediately and 3 hr after surgery for combing KIM-1, NAG and NGAL	Single center study and small sample size. No standard procedure to combine the multiple biomarkers
Liangos et al[58]	Adult cardiac surgery patients (n = 103)	Prospective study (uKIM-1 and others)	AUC-ROC of 0.78 at 2 hr after surgery	Single center study and small sample size
Contrast induced nephropathy				
Malyszko et al[47]	Adult patients for cardiac catheterization (n = 140)	Prospective study (uKIM-1 and others)	No statistically significant KIM-1 elevation in CIN group	Single center study No information on severity and outcome of CIN

Abbreviations: AKI, acute kidney injury; AUC-ROC, area under the receiver operating characteristic curve; CIN, contrast-induced nephropathy; KIM-1, kidney injury molecule-1; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; uKIM-1, urinary kidney injury molecule-1.

expression patterns of uKIM-1 for the early detection of AKI, or to elucidate how this temporal course relates to the onset, severity, and outcome of AKI.

Interleukin-18

IL-18 is a pro-inflammatory cytokine and has been shown to be involved in mediating inflammation in many organs.[59–61] Renal IL-18 mRNA levels are significantly upregulated in the proximal tubules following ischemia-reperfusion injury, autoimmune nephritis, and cisplatin-induced nephrotoxicity.[62] IL-18 is induced and cleaved in the proximal tubule, and can be detected in urine following ischemic AKI in animal models.[63]

The diagnostic utility of uIL-18 was evaluated for the early detection of postoperative AKI after pediatric cardiac surgery in a case control study,[64] using samples from the same cohort in the NGAL study previously described.[33] In that study, uNGAL was measured and found to have AUC-ROC values of 0.99 and 1.00 at 2 and 4 hours, respectively, following CPB. A subsequent study using all of the AKI cases and under half of the non-AKI cases showed that uIL-18 has AUC-ROC values of 0.61 at 4 hours, 0.75 at 12 hours, and 0.73 at 24 hours following CPB for the prediction of AKI (Table 4). Parikh et al[35] reported that uIL-18 had an AUC-ROC value of 0.74, while the clinical prediction model for AKI had an AUC-ROC value of 0.69 after cardiac surgery in adult patients. uIL-18 performed similarly for the early detection of AKI after cardiac surgery among pediatric patients.[36] However, in a single-center prospective study of 100 adult

patients, uIL-18 performed poorly, with an AUC-ROC value of 0.53–0.55 at two time points after cardiac surgery.[65]

IL-18 also associated as a predictor biomarker for AKI in pediatric and adult critically ill patients (Table 4). In a prospective study of 138 patients with acute respiratory distress syndrome, elevated uIL-18 levels in the AKI group preceded the elevation of SCr by 1–2 days, with an AUC-ROC value of 0.73, and was an independent predictor of death in this cohort.[66] Washburn et al[67] also demonstrated among pediatric patients that uIL-18 was elevated about 2 days prior to the rise in SCr, but that the AUC-ROC value was 0.54 for predicting AKI development within 24 hours.

Overall, there have been very few studies done to validate the temporal expression patterns of uIL-18 for the early detection of AKI, or to elucidate how this temporal course relates to the onset, severity, and outcome of AKI.

Conclusion

The ultimate goal of a more sensitive AKI biomarker or panel of AKI biomarkers is improved early detection and monitoring of AKI, which will lead to improved outcomes through earlier therapeutic intervention and the re-evaluation of other pharmacologic agents that have shown promise in experimental animal models. The search for new AKI biomarkers has been evolving rapidly with advancements in modern technologies. Recently, several protein biomarkers, including KIM-1, NGAL, IL-18, cystatin C, and L-fatty acid binding protein, have emerged through the application of functional genomics and proteomics to human and ani-

Table 4 Prospective studies of IL-18 for early detection of AKI

Clinical study	Study population	Type of study	Major findings	Limitations
Cardiac surgery				
Parikh et al[64]	Pediatric cardiac surgery patients (n = 55)	Prospective study (uIL-18)	AUC-ROC of 0.61, 0.75, 0.73 at 4 hr, 12 hr, and 24 hr after surgery, respectively	Single center study and small sample size
Haase et al[65]	Adult cardiac surgery patients (n = 100)	Prospective study (uIL-18)	AUC-ROC of 0.53 at arrival to ICU after surgery	Single center study and small sample size
Parikh et al[35,36]	Adult (n = 1219) and pediatric (n = 311) cardiac surgery patients	Prospective multi-centered study (uIL-18 and others)	AUC-ROC of 0.74 (adult) and 0.72 (children), respectively	
Critical care				
Parikh et al[66]	Adult critically ill patients (n = 138)	Prospective study (uIL-18)	AUC-ROC of 0.73 for predicting AKI development within 24 hr	Excluded 479 out of 617 patients in ARDS network trial
Washburn et al[67]	Pediatric critically ill patients (n = 137)	Prospective study (uIL-18)	AUC-ROC of 0.54 for predicting AKI development within 24 hr	Single center study and small sample size

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AUC-ROC, area under the receiver operating characteristic curve; ICU, intensive care unit; IL-18, interleukin-18; uIL-18, urinary interleukin-18.

mal AKI models. However, several requirements must be met for their use in daily clinical practice. AKI biomarkers must ideally allow for the early detection of kidney injury, identify the severity of the AKI, provide a rationale for risk stratification for clinical studies including the identification of patients at risk for AKI, guide the timing of therapy, reflect the improvement and worsening of the kidney injury, and be amenable to quick and reliable measurement at the bedside or in the clinical laboratory.

Available studies have highlighted several limitations of new AKI biomarkers in the early detection and prediction of AKI; these limitations preclude the mainstream acceptance of AKI biomarkers in the clinical setting. Most of the human studies come from single centers and from homogeneous patient populations. Most studies assessing AKI exclude CKD patients. Most AKI cases were not severe injuries based on the rapid reversibility of SCr, and only a limited number of AKI patients required RRT. Existing studies have been insufficiently powered to establish a cutoff value that is predictive of AKI, especially with severe injury. There is presently limited data available regarding the utility of biomarkers for differentiating causes of AKI. Furthermore, the heterogeneity of AKI and existing published data suggest that more than one biomarker may be necessary to obtain sufficient sensitivity and specificity for the early detection of AKI. There is emerging evidence that combining multiple biomarkers may allow for the early detection of AKI.[29,57] However, there is currently no standard way to combine multiple biomarkers for clinical use. It also remains unclear if combining biomarkers will provide a sufficiently high sensitivity to provide clinically useful, predictive information over the use of SCr alone.

Larger prospective multicenter studies are absolutely necessary to validate the temporal expression patterns of various AKI biomarkers for the early detection of AKI, and to elucidate how this temporal course relates to the onset, severity, and outcome of AKI. However, the evaluation of the performance of AKI biomarkers is inherently flawed because there is currently no standard definition of AKI that is not based on a change in SCr. The use of an imperfect SCr in the authors' definition of AKI can lead to poor performance by AKI biomarkers.[68] The main question, then, is how to define the AKI without depending on SCr. One possible option is to define the AKI based on the profile of multiple biomarkers that are sensitive to renal tubular injury. However, this approach needs further study to address several issues. First, we need a histopathologic evaluation of the kidney in order to directly relate the biomarkers to injury, but routine renal biopsy in AKI patients is not feasible, and there can be dissociation between structural changes and functional decreases in AKI. Second, we need to investigate the clinical relevance of subclinical alterations in renal function detected by urinary biomarkers without overt changes in SCr.[69–72] So far there have been no pathologic evaluations of the kidney among patients with subclinical AKI. Third, more information must be gathered regarding the accuracy of biomarker measurements in the presence of interfering substances and the stability of the various biomarkers in routine clinical storage conditions, including a number of freeze-thaw cycles. Fourth, it is known that the measurements of AKI biomarkers can be influenced by systemic inflammation, infection, the patient's age, malignancy, and CKD. Finally, we need standardization for the measurement of biomarkers. Until a better AKI definition is available, we continue to be cautious of interpretations of reported AKI biomarkers' performance.

Once a more sensitive biomarker or panel of biomarkers for AKI is validated for clinical use, the next challenging tasks are the development of a POC and the selection of a suitable patient group for pharmacologic treatment. POC will provide a quick and reliable measurement at the bedside or in clinical laboratory for the detection of AKI. Multiple therapeutic possibilities that showed promise in animal studies but failed in human studies can then be revisited in clinical trials. However, it is critical to know the timing of the kidney insult because previous animal studies and failed attempts of human intervention in clinical trials clearly demonstrate that the introduction of treatment should precede the rise of SCr and be very early after the insult. This will greatly limit the utility of AKI biomarkers and potential pharmacologic treatments to patients with hospitalized AKI, including postoperative or contrast-dye-induced AKI.

Despite the early promise of new AKI biomarkers for the early detection of AKI, there is no clear evidence that current AKI biomarkers demonstrate a clear benefit over traditional approaches in clinical decision-making in patients with AKI. More studies with better biomarkers are required to establish their utility in daily clinical practice.

Disclosure

The author reports no conflicts of interest in this work.

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