Mini-Review

Clinical Utility of Biomarkers of AKI in Cardiac Surgery and Critical Illness

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Summary

AKI is a common and serious complication that is associated with several adverse outcomes in hospitalized patients. The past several years have seen a large number of multicenter investigations of biomarkers of AKI in the setting of cardiac surgery and critical illness. This review summarizes these biomarker results to identify applications for clinical use. The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study showed that blood and urine biomarkers measured preoperatively, immediately postoperatively, and at the time of the clinical increase in serum creatinine in the setting of cardiac surgery all had the ability to improve patient risk stratification for a variety of important clinical end points. Analyses of biomarkers concentrations from the Acute Respiratory Distress Syndrome Network, EARLY ARF, and other studies of critically ill subjects have similarly shown that biomarkers measured early in the clinical course can forecast the development of AKI and need for renal replacement therapy as well as inpatient mortality. Although biomarkers have informed the diagnosis, prognosis, and treatment of AKI and are inching closer to clinical application, large multicenter interventional clinical trials to prevent AKI using biomarkers should continue to be an active area of clinical investigation.

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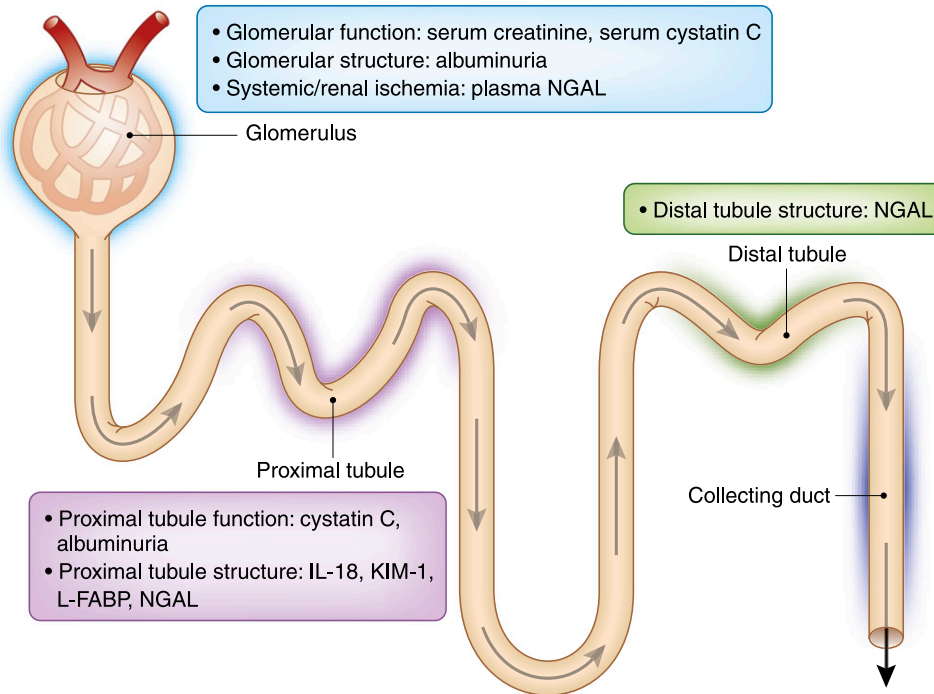
Background

For over a century, the measurement of serum creatinine, a biomarker of glomerular filtration, has been a mainstay of clinical laboratory testing and served as the primary method for quantifying of renal function (1). Over the decades, the interpretation of serum creatinine in the setting of chronic and AKI has been refined by the implementation of estimating equations and classification schemas (2–6). These creatinine-based estimates of renal function are focused on glomerular filtration and do not adequately account for structural renal tubular injury, which may be extensive in the setting of AKI. The past several years have seen a large number of investigations seeking novel biomarkers of AKI. In this review, we discuss the results of larger multicenter observational studies and interventional trials investigating the clinical use of several biomarkers of AKI in clinical settings of cardiac surgery and critical illness. This article includes all relevant studies through October 2012.

Novel biomarkers of AKI originally sought to replace serum creatinine, which suffers diagnostically in that it may not be elevated until days after kidney injury (7). Recently, several in-depth reviews have attempted to summarize these investigations (8,9). Figure 1 displays a nephron highlighting the segments where several functional and structural biomarkers of AKI have been shown to be constitutively expressed or induced in the setting of injury. Currently, in the United States, no novel biomarker is approved by the Food and Drug Administration as a clinical tool for the detection or diagnosis of clinical

human AKI; however, several countries in Europe and Asia have approved a variety of different biomarkers for clinical use.

AKI Associated with Cardiac Surgery

Cardiac surgery has long been used to study AKI because of the opportunity to prospectively follow patients before and after a well timed ischemic renal insult (cardiopulmonary bypass). For this reason, several blood urinary proteins have been investigated in this setting and found to serve as biomarkers of AKI after cardiac surgery, including neutrophil gelatinase-associated lipocalin (NGAL) (10–14), IL-18 (15), cystatin C (CysC) (13,16), kidney injury molecule-1 (KIM-1) (12,16), and liver fatty acid binding protein (17). Many of these previously published studies are limited in that they are small single-center studies with low severe AKI event rates (10–17). However, within the last year, data from the first large international, prospective observational study investigating biomarkers after cardiac surgery have been published (18–22). The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE AKI) study assembled a cohort of 1219 adults undergoing coronary artery bypass grafting and/or valvular surgery cardiac surgery and 311 children undergoing surgery for congenital cardiac lesions. The study's primary objective was to determine whether early preoperative and postoperative measures of biomarkers could predict which patients would develop clinical AKI and other adverse outcomes after cardiac surgery. Subjects

Figure 1. | Biomarkers of AKI: anatomic site along the nephron. This figure summarizes the biomarkers of AKI discussed in this paper and stratifies them according to their anatomic site of action. Biomarkers found in the blood are accounted for at the glomerulus and stratified as biomarkers of functional, structural, or ischemic renal injury. Urinary biomarkers are mapped along the nephron and stratified as biomarkers of functional or structural renal tubular injury.

had preoperative blood and urine samples collected and postoperative blood collected at the time of intensive care unit (ICU) arrival and then daily for the next 5 days, whereas urine was collected four times during the first postoperative day and then daily until day 5, with samples being collected, frozen, and stored for batched biomarker measurement.

Preoperative Biomarkers

In the adult cohort, preoperative serum CysC performed better than creatinine or creatinine-based estimated GFR (eGFR) at forecasting the risk of AKI, defined by Acute Kidney Injury Network (AKIN) stage 1, CysC was categorized into quintiles (Qs) and grouped into categories (low [Q1 and Q2], intermediate [Q3 and Q4], and high [Q5]). The adjusted odds ratios for Q3 and Q4 (combined) and Q5 of CysC were 1.9 (95% confidence interval [CI]=1.4 to 2.7) and 4.8 (95% CI=2.9 to 7.7) compared with 1.2 (95% CI=0.9 to 1.7) and 1.8 (95% CI=1.2 to 2.6) for creatinine and 1.0 (95% CI=0.7 to 1.4) and 1.7 (95% CI=1.1 to 2.3) for creatinine-based eGFR, respectively. Thus, in adults, as a filtration marker, preoperative serum CysC offers additional information in prediction of postoperative AKI and could be included in future risk stratification systems (21). Serum CysC was also measured in the pediatric cohort. In unadjusted analyses, higher preoperative serum CysC predicted postoperative stages 1 and 2 AKI, but this association was attenuated after adjusting for clinical factors known to impact AKI.

In addition to measuring preoperative CysC, TRIBE AKI measured preoperative albuminuria in 1159 adult patients.

The cohort was organized into clinical risk categories based on the preoperative urine albumin to creatinine ratio (ACR): 10 mg/g or less (≤1.1 mg/mmol), 11–29 mg/g (1.2–3.3 mg/mmol), 30–299 mg/g (3.4–33.8 mg/mmol), and 300 mg/g or greater (≥33.9 mg/mmol). The incidence of AKI, defined as AKIN stage 1, increased across the ACR categories, with those patients in the >300 mg/g group having a relative risk (RR) of 2.36 (95% CI=1.85 to 2.82) compared with the patients in the <10 mg/g group. This association was slightly attenuated after adjusting for variables known to impact proteinuria and AKI (RR=2.21 [95% CI=1.66 to 2.73]) (20). These adult data are in contrast to pediatric TRIBE AKI data (n=294), which showed no association between preoperative ACR and the development of postoperative AKI (defined as either AKIN stage 1 or a doubling of serum creatinine or receipt of renal replacement therapy [RRT]) (23). The adult ACR data represent an additional biomarker to aid in cardiac surgery AKI prediction models and supplement other recent data that point to proteinuria/albuminuria serving as a biomarker of AKI in the pre- and postoperative settings (17,24).

Finally, preoperative brain natriuretic peptide (BNP), a biomarker of hemodynamic stress, cardiovascular disease, and heart failure, was measured in the adult cohort. In analyses adjusted for preoperative characteristics, preoperative BNP was a strong and independent predictor of mild (AKIN stage 1) and severe (twofold increase in creatinine from baseline or need for RRT) AKI. Compared with the lowest BNP quintile, the highest quintile had a significantly higher risk of mild AKI (RR=1.87 [95%

CI=1.40 to 2.49]) and severe AKI (RR=3.17 [95% CI=1.06 to 9.48]). After adjustment for clinical predictors, addition of BNP significantly improved the area under the curve (AUC) to predict mild AKI (0.67–0.69, P=0.02) but not severe AKI (0.73–0.75, P=0.11). The continuous net reclassification index (NRI) for BNP to predict at least AKIN stage 1 was 0.18 (0.06–0.31), with the majority of this relatively small association coming from the ability of BNP to appropriately classify those patients who did not have mild AKI (0.151; 0.07–0.23). However, the continuous NRI for detecting severe AKI was not significant. Preoperative BNP levels may identify patients with subclinical heart failure and improve AKI risk stratification and discrimination among surgical candidates (25).

Postoperative Biomarkers

In the adult population, urine IL-18 and urine and plasma NGAL levels peaked within 6 hours of ICU arrival, which was well before increases in serum creatinine (24–72 hours postoperative) (18). In the adult population, the highest quintiles of urine IL-18 and plasma NGAL were associated with an adjusted 6.8-fold (95% CI=1.9 to 24.3) and 5.0-fold (95% CI=1.6 to 15.3) higher odds of AKI, defined as doubling of serum creatinine or receipt of RRT, compared with the lowest quintiles. The clinical prediction model for AKI, which had an AUC of 0.69, was based on the Society of Thoracic Surgeons (STS) risk prediction model (26), which included age, sex, race, diabetes, hypertension, preoperative renal function, cardiopulmonary bypass pump time, and nonelective procedures. Individually, urine IL-18 and plasma NGAL significantly improved the AUC to 0.76 and 0.75, respectively. Elevated urine IL-18 and urine and plasma NGAL levels were all separately associated with longer length of hospital stay, longer ICU stay, and higher risk for dialysis or death. The categorical NRI values for IL-18 and plasma NGAL (SEM) were 0.25 (0.10), P=0.01 and 0.18 (0.09), P=0.05, showing that both biomarkers improved reclassification when added to the clinical model. In this adult cohort, none of the quintiles of urine NGAL were independently associated with AKI, and the addition of urine NGAL to the clinical model did not improve the AUC (18).

Similar to the adult cohort, urine IL-18 and urine and plasma NGAL levels in the pediatric patients peaked within 6 hours of ICU arrival, significantly preceding serum creatinine (24–48 hours postoperative) (19). In the pediatric cohort, the first postoperative urine IL-18 and urine NGAL levels strongly associated with severe AKI, defined by receipt of dialysis or doubling in serum creatinine during hospital stay. After multivariable adjustment, the highest quintile of urine IL-18 and urine NGAL associated with 6.9- (95% CI=1.7 to 28.8) and 4.1-fold (95% CI=1.0 to 16.3) higher odds of AKI, respectively, compared with the lowest quintiles. Elevated urine IL-18 and urine NGAL levels associated with longer hospital stay, longer ICU stay, and prolonged duration of mechanical ventilation. The accuracy of urine IL-18 and urine NGAL for diagnosis of severe AKI was moderate, with AUCs of 0.72 and 0.71, respectively. In this pediatric cohort, none of the quintiles of plasma NGAL were independently associated with the development of postoperative severe AKI (19). Finally, serum CysC was measured in this pediatric cohort

within 6 hours postoperatively, portending an increased odds of both AKIN stages 1 (odds ratio [OR]=6.0 [95% CI=1.5 to 23.3]) and 2 (OR=17.2 [95% CI=1.6 to 189.3]) (22).

Urinary albumin concentrations (milligrams per liter) and dipstick proteinuria values within 6 hours of adult cardiac surgery also correlated with the future development of AKI. Compared with the lowest quintile, the highest quintile of albuminuria (defined as the urinary albuminuria measured within the first 6 postoperative hours) and highest group of dipstick proteinuria were associated with the greatest risk of AKI (adjusted RR=2.97 [95% CI=1.20 to 6.91] and adjusted RR=2.46 [95% CI=1.16 to 4.97], respectively). However, only postoperative urine albumin was associated with improved risk stratification when added to the clinical model (AUC increased from 0.75 to 0.81, P=0.006). Despite its known use in other settings, a higher early postoperative ACR (milligrams per gram) was not statistically associated with AKI risk. The poor performance of ACR in the context of adult cardiac surgery may be explained by variations in the urine creatinine excretion within and between individuals, which could be especially prominent when renal function is not in a steady state. Lastly, as discussed above, adults with postoperative AKI had higher levels of albuminuria and a higher ACR preoperatively and on all postoperative measures compared with patients who did not develop AKI.

In contrast, urine ACR (milligrams per gram) and not albuminuria (milligrams per liter) was found to be predictive of AKI in the pediatric cohort. In children<2 years, an absolute first postoperative ACR≥908 mg/g (103 mg/mmol, highest tertile) predicted the development of AKIN stage 2 or 3 AKI with an adjusted RR=3.4 (95% CI=1.2 to 9.4) compared with the first tertile. In children≥2 years, a postoperative ACR≥169 mg/g (19.1 mg/mmol, highest tertile), regardless of preoperative values, predicted stage 1 AKI after adjusting for clinical factors such as age, race, sex, preoperative eGFR, and type of cardiac surgery (adjusted RR=2.1 [95% CI=1.1 to 4.1]) (23). Although urine albumin and ACR remain established and readily available laboratory tests, the diversity of results when investigating the development of postoperative AKI indicates that additional studies are needed before it may be used in clinical practice.

Biomarker-Assisted Prognosis at the Time of Clinical AKI

Samples from the TRIBE AKI adult cohort were used to determine whether kidney injury biomarkers can forecast AKI severity and AKI progression at the time of the first clinical diagnosis of early AKI. Biomarkers were measured on the day of AKI diagnosis in 380 patients who developed at least AKIN stage 1 AKI. Progression of AKI, defined by worsening of AKIN stage (e.g., stage 1 to stage 2 or more) occurred in 45 patients (11.8%). Sixty-six percent of patients developed AKI within the first 2 postoperative days; 93.4% of patients developed AKI by day 3. At the time of creatinine-based AKI diagnosis, each biomarker was categorized into quintiles and grouped into categories (low [Q1 and Q2], intermediate [Q3 and Q4], and high [Q5]). Using multivariable logistic regression and adjusting for clinical predictors, including postoperative serum creatinine, the risk of AKI progression in the high category, compared with the low category, was significantly elevated for three biomarkers: urine IL-18 (OR=3.0 [95%

CI=1.3 to 7.3]), urine ACR ratio (OR=3.4 [95% CI=1.3 to 9.1]), and plasma NGAL (OR=7.7 [95% CI=2.6 to 22.5]). Each biomarker provided improvement in risk classification over serum creatinine and the clinical model alone. This ability to anticipate clinical prognosis at the time of creatinine elevation represents novel data as well as an exciting new use for biomarkers of AKI (27).

Although this large-scale, international, prospective observational study did not provide a perfect biomarker to predict early AKI or AKI severity, it has improved our diagnostic ability for AKI at several clinically relevant time points and serves as a model for future large-scale biomarker investigations. It is important to recognize that this study was not without limitations, including low incidence of major adverse kidney events (RRT and death), the multifactorial nature of AKI after cardiac surgery (ischemia, nephrotoxin, inflammation, and intravascular-mediated processes may all play a role), and the imprecision of using serum creatinine (which suffers from hemodilution in the postoperative setting) as the gold standard definition for AKI. Figure 2 summarizes the results from the TRIBE AKI cohorts for biomarkers across various time points of clinical risk prediction. With the long-term follow-up of these patients (3–5 years after surgery) currently being conducted, the TRIBE AKI consortium has established a large-sample biorepository and clinical research information system that will permit access to this well phenotyped cohort for future investigations of AKI in the setting of cardiac surgery.

Biomarkers in the Setting of Critical Illness and Sepsis

Sepsis is a common cause of AKI, accounting for almost one half of all AKI cases in critically ill patients. Approximately 30% of those patients have community-acquired

sepsis with complication of AKI (28–31). Not surprisingly, there have been several investigations into the performance of biomarkers in diagnosing early and severe AKI in the setting of sepsis/critical illness. As with cardiac surgery, the majority of this published work represents small single-center studies that will require validation in large multicenter investigations. We highlight below a few of the larger critical care and sepsis studies, some of which were *posthoc* analyses of larger multicenter studies (32,33).

In a *posthoc* analysis of the EARLYARF study, a prospective observational study in two large general ICUs (n=444), Nejat et al. (32) showed that urinary CysC (UCysC) levels were elevated in the setting of sepsis (n=125) and AKI (n=81). After adjusting for clinical covariates known to impact critical illness and AKI, UCysC levels were independently associated with sepsis (OR=3.43 [95% CI=2.46 to 4.78]), AKI (OR=1.49 [95% CI=1.14 to 1.95]), and mortality (OR=1.60 [95% CI=1.16 to 2.21]) (32). Note, in this study, that there was no interaction between sepsis and AKI and that these findings are in line with smaller studies that investigated the ability of UCysC to detect early AKI and predict the need for RRT and death in a mixed surgical and medical ICU population (34,35).

IL-18, which is upregulated in the setting of ischemia-induced AKI, has shown mixed results in the setting of sepsis and critical illness-related AKI. In a nested case control study of 138 patients with Acute Respiratory Distress Syndrome (ARDS) from the multicenter randomized controlled ARDS-Net study, urine IL-18 levels were elevated 24–48 hours earlier than serum creatinine in those patients with ARDS and AKI. A urine IL-18 level>100 pg/ml was associated with increased odds of AKI of 6.5 (95% CI=2.1 to 20.4) in the next 24 hours (33). Additionally, levels were statistically different between survivors and
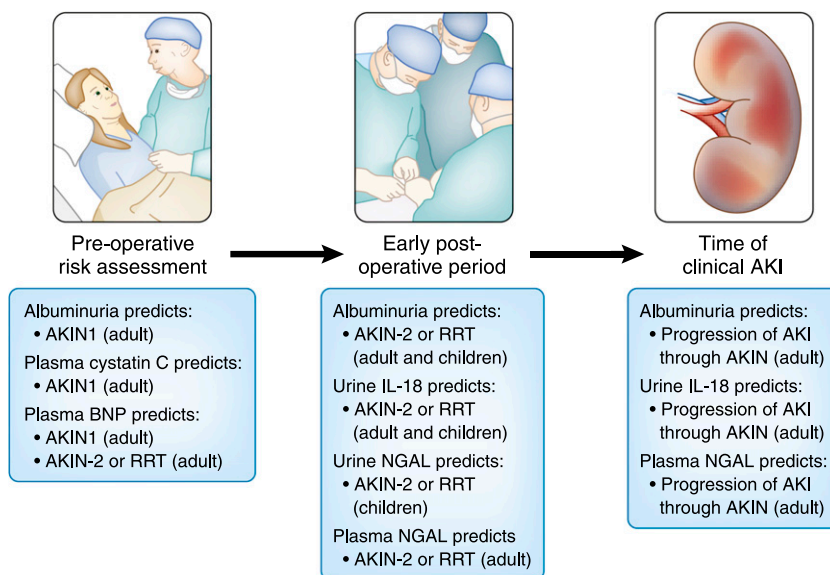

Figure 2. | Clinical timeline of biomarker risk stratification in cardiac surgery. This figure summarizes the findings to date of the Translational Research Investigating Biomarker Endpoints in AKI study (TRIBE AKI) Consortium with regards to the performance of biomarkers after adult and pediatric cardiac surgery. A variety of biomarkers were interrogated at several clinically relevant time points to determine their ability to prognosticate AKI outcomes. The outcomes that the biomarkers predict are given as bullets below each biomarker. The cohorts are given in parenthesis.

nonsurvivors. However, in a follow-up single-center study of 451 patient admitted to the ICU, urinary IL-18 levels at the time of ICU admission did not predict the future development of AKI (AKIN stage 1) but did correlate with other adverse patient outcomes (OR=1.86 [95% CI=1.31 to 2.64]) for the prediction of death or dialysis (36). Although mortality results are consistent, additional studies are required to clarify results predicting AKI.

Urine NGAL has shown promising results in predicting AKI and patient mortality in the setting of ICU admission/critical illness (35,37). In the EARLYARF study, urine NGAL (n=489) on admission to the ICU displayed modest ability to predict the future development of AKI, defined as AKIN stage 1 (AUC [95% CI]=0.66 [0.60 to 0.72], $P<0.001$); however, it performed even better in the prediction of receipt of RRT within the first 7 days (AUC [95% CI]=0.79 [0.65 to 0.94], $P<0.001$). These results are in line with two large single-center studies. In the first study (n=451), Siew et al. (37) used Cox proportional hazard models to show that urine NGAL was able to predict AKI within 24 hours of ICU admission (AUC of 0.71) and an independent risk factor for time to first RRT treatment (hazard ratio=2.60 [95% CI=1.55 to 4.35]). In a second single-center study (n=632), urine NGAL on admission was shown to have an AUC (AUC±2 SEM) of 0.80±0.04 for the future development of RIFLE risk and an AUC of 0.89±0.04 for the prediction of RRT (n=280) (38). Finally, in a separate single-center study higher urine NGAL levels correlated with higher urine microscopy injury scores ($P<0.001$) and predicted worsening (defined as progression through the RIFLE stages) in the setting of septic AKI (39).

Plasma NGAL has been measured in many of these same studies and shown mixed results in its ability to forecast AKI within the first 24–48 hours of ICU stay (38,40). Interestingly, plasma NGAL has been shown to predict recovery from AKI. In a posthoc analysis of a multicenter, prospective, cohort study of patients with community-acquired pneumonia (n=181), lower plasma NGAL predicted renal recovery (AUC=0.74) (41). Although NGAL did not outperform the clinical model in this study, it offers a first glimpse into the ability to predict renal recovery and requires validation in a larger prospective study.

In addition to the wealth of data supporting the role of biomarkers in forecasting the development of AKI, there are emerging data that, in the setting of critical illness, biomarkers may correlate with the reversibility and duration of AKI. In a separate posthoc analysis of the EARLY ARF study, Nejat et al. (42) showed that concentrations of UCysC, urinary KIM-1, and IL-18 were statistically different in those patients with prerenal AKI, defined as AKIN stage 1 with recovery in 48 hours and a fractional excretion of sodium of <1%, compared with concentrations in those patients with no AKI as well as those patients with AKIN stage 1 that lasted >48 hours (intrinsic AKI). These biomarkers displayed a progressive increase across the spectrum of AKI (no AKI < prerenal < intrinsic). Although the definition of prerenal AKI used is not universally accepted, this investigation of a mixed medical–surgical ICU population corroborates a previous single-center study that showed that biomarkers may help distinguish between prerenal and intrarenal causes of AKI (43). Our hope is that, in the near future, investigations move away from nonstandardized

and potentially confusing terms such as prerenal and view kidney injury in terms of biomarkers of functional and structural damage. Finally, additional posthoc analyses of the EARLYARF cohort showed that the ability of biomarkers to detect AKI varied according to a subject's baseline kidney function, with biomarkers performing better in those patients with higher and near-normal baseline GFRs (35).

This ability to potentially discriminate the diagnostic and prognostic aspects of AKI has led some to investigate AKI biomarkers for their ability to augment, rather than replace, serum creatinine. Haase et al. (44) conducted a pooled prospective study (n=2322; 1452 with cardiac surgery and 870 with critical illness) that designated subjects as NGAL(+) or NGAL(−) and creatinine(+) or creatinine(−) (AKI was defined as RIFLE-R). After analyzing NGAL data from 10 separate prospective observational studies, Haase et al. (44) showed that individuals who were NGAL(+) but creatinine(−) needed acute dialysis over 16 times more often than those individuals that were NGAL(−) creatinine(−) (OR [95% CI]=16.4 [3.6 to 76.9], $P<0.001$) (44). The study also showed an incremental increase in ICU stay, hospital stay, and mortality among the four study groups as follows: NGAL(−) creatinine(−) < NGAL(+) creatinine(−) < NGAL(−) creatinine (+) < NGAL(+) creatinine(+). Detecting adverse patient outcomes, in the absence of significant changes in serum creatinine, is a paradigm shift for nephrologists, and this association was recently replicated through measurements of urine NGAL, urine KIM-1, and CysC in the clinically distinct setting of the Emergency Department (45). Regardless of the clinical setting, these findings will need to be validated in follow-up studies but represent alternative and clinically relevant uses for biomarkers of renal injury.

As described above, baseline renal function has been shown to impact a biomarker's ability to detect AKI in a variety of clinical settings (35,46). However, for several biomarkers, some clinical variables, outside of renal function, have been shown to impact biomarker concentrations and affect their ability to detect clinical end points. In a posthoc analysis of those individuals in the control arm of the EARLYARF study (subjects not receiving erythropoietin), Nejat et al. (32) showed that, in addition to forecasting the development of AKI at ICU admission, UCysC levels (milligrams per liter) were significantly higher in those individuals with sepsis (n=363; 2.45 [0.26 to 10.7]) compared with those individuals without sepsis (n=363; 0.08 [0.03 to 0.24]) (32). Similarly, in a study of 83 patients with AKI, plasma and urine NGAL values within the first 24 hours of ICU admission were higher in those patients with septic AKI (n=43) compared with nonseptic AKI (n=40) (40). In both of these examples, the concomitant presence of sepsis with AKI led to higher biomarker concentrations and supports the notion that additional studies will be needed to quantify the impact of comorbidities on biomarker values. Thus, based on our current knowledge, we anticipate the need for separate cutoff values for individual biomarkers depending on specific clinical scenarios.

Clinical Use of AKI Biomarkers: Moving Forward

With the completion of large multicenter biomarker studies, we will further our knowledge of the role of these

diagnostic tools in specific clinical settings. In the near future, we anticipate that these investigations will include a combination of clinical risk factors and multiple biomarkers to predict the clinical course and prognosis. To date, several investigations have sought to combine AKI biomarkers with clinical information to determine if the addition of the novel marker improves risk stratification (18,19,27,36–38). Few studies have incorporated preexisting standardized clinical models/scores (*e.g.*, Acute Physiology, Age, Chronic Health Evaluation [APACHE] or Mehta Score for cardiac surgery) (47), because most of these risk stratification scores were constructed and validated to detect end points other than nondialysis-requiring AKI (26). Using scoring systems and risk models developed for critical illness (*e.g.*, APACHE and Sequential Organ Failure Assessment score) for AKI has not had broad success, compelling many AKI investigators (including the TRIBE cohort) to create their own *de novo* clinical risk models based on relevant variables known to impact AKI rates. Given the emerging data on preoperative novel biomarkers, we foresee future preoperative AKI risk stratification scoring systems including biomarkers; however, at the current time, no such criteria, for any clinical setting, have been created/validated.

Lastly, the ability to combine biomarkers themselves, irrespective of traditional clinical data, is another area of intense investigation. Unfortunately, as of today, standard statistical approaches to evaluate biomarker combination effects on risk prediction are inadequate. Standard methods apply to dichotomous outcomes, whereas AKI is often broken down according to diagnostic criteria and has four states (*e.g.*, no AKI and AKIN stages 1–3). Additionally, standard methods and changes in AUC and NRI do not account for sampling variability in regression coefficients and have been shown to provide incorrect *P* values and CIs (48,49). In the near future, novel methods including ordinal logistic regression for developing combinations of clinical variables with or without biomarker values for predicting multiple disease states will be developed, but

until such time, we remain reliant on imperfect measures such as change in AUC.

Clinical Trials—The Future of Biomarkers

The EARLYARF study has set the foundation for future studies to use AKI biomarkers to serve as the interventional trigger in clinical trials (50). In the near future, we anticipate many more clinical trials using biomarkers in a variety of clinical settings. It is conceivable that, based on their ability to predict the future need for RRT or severe AKI, biomarkers could be used to help refine a high-risk population to randomize subjects to early versus late RRT initiation in the setting of cardiac surgery or critical illness. Similarly, biomarkers may also reduce the misclassification of AKI patients in future therapeutic trials if shown to be diagnostic of more severe forms of AKI (not necessarily requiring RRT); biomarkers may help distinguish those patients with transient (<48 hours) and sustained AKI. This ability to assist in the differential diagnosis of AKI (prerenal versus acute tubular necrosis) would be crucial in limiting the number of patients needed per study, because inclusion of patients who may not have progressed to the desired end point increases the total number of patients required to conduct an appropriately powered study. Thus, future clinical trials of AKI interventions could be targeted to those patients at highest risk, which would be far more efficient in terms of costs and resources. Finally, biomarkers, in concert with clinical factors, should also be used to reinvestigate previously studied therapeutic agents that were not shown to be effective in the setting of late AKI or outdated diagnostic/inclusion criteria (51,52). However, the use of these biomarkers needs to be framed according to the size and scope of the intended study, because at this time, it seems appropriate for change in biomarkers concentration to serve as secondary end points of smaller therapeutic-based pilot studies.

Recently elevated urine NGAL and IL-18 in the early postoperative period after renal transplantation have been

Table 1.   Biomarker performance from multicenter studies at a variety of clinical time points in cardiac surgery and critical illness

	Cardiac Surgery			Critical Illness/Sepsis		
	Preop AKI Risk Assessment	Early Postop Diagnosis of AKI	AKI Progression	Early Diagnosis of AKI	Classification of AKI (Transient Versus Intrinsic AKI)	Prediction of Dialysis
U NGAL	N/A	+	−	+	+	+
B NGAL	−	+	+	−	?	−
U CysC	N/A	−	−	+	+	+
U IL-18	N/A	+	+	+	+	+
U KIM-1[a]	N/A	+	−	+	−	−
U protein/ albumin	+	+	+	?	?	?

Preop, preoperative; postop, postoperative; NGAL, neutrophil gelatinase-associated lipocalin; N/A, not applicable (biomarkers of tubular injury have no role in preoperative risk screening); +, data published displays the ability to detect this aspect of AKI; −, data published does not display the ability to detect this aspect of AKI; ?, no large multicenter data published on this biomarker/aspect of AKI; B, blood CysC, cystatin C; KIM-1, kidney injury molecule-1; U, urine.
[a]KIM-1 data from the TRIBE-AKI study are under review.

shown to correlate with poor graft function at 1 year (53). As investigators continue to study the long-term outcomes of hospitalized subjects with AKI, (*e.g.*, the development of CKD and other adverse patient events), there may be an opportunity for biomarkers of AKI to detect both the acute inpatient tubular injury as well as the more chronic outpatient process (54). Based on this limited published data with long-term outcomes, it is feasible that the change in biomarker values in the perioperative/early ICU admission period seen in an interventional trial may serve as a meaningful secondary end point in future studies. This way is yet another way that biomarkers of AKI may move from being a clinical valid tool to a clinically useful test.

Summation

Based on the current evidence, it seems that traditional biomarkers, such as albuminuria, and some novel biomarkers may be helpful across several clinical scenarios, such as preoperative risk assessment, early detection of AKI (before changes in serum creatinine), detection of severity of AKI (need for RRT), and prediction of AKI duration. Each individual type of AKI has its own distinct pathophysiologic (and biomarker) fingerprint; for example, the biomarkers that diagnose and prognosticate ischemia-reperfusion AKI may be different from those biomarkers that detect sepsis-associated AKI or those biomarkers that forecast radio contrast-associated AKI. Similarly, every biomarker has its own distinctive kinetics, and accordingly, certain individual biomarkers may excel in detecting early AKI, whereas others may help prognosticate outcomes at the time of creatinine elevation (46). To date, several individual biomarkers have excelled at detecting multiple aspects of AKI in the setting of both cardiac surgery and critical illness. Table 1 summarizes published data from large cardiac surgery and critical illness multicenter studies regarding individual biomarkers and a variety of facets of AKI.

Despite the promise and progress that biomarkers have displayed over the last several years, the full use of biomarkers in the setting of critical illness and cardiac surgery remains unknown. Over the next few years, multicenter studies will complete longer follow-up studies, highlighting additional roles of biomarkers and quantifying the impact of structural injury to the kidney with regards to long-term mortality and AKI. Additionally, future investigations of biomarkers will seek to further expand our knowledge of clinical factors that may impact biomarker concentrations (*e.g.*, comorbid conditions, such as CKD or hypertension, or medication usage, such as vasoactive medications or renin-angiotensin-aldosterone agents). Furthermore, it is reasonable to expect more interventional trials that use biomarkers, because both the trigger for therapeutic intervention in the setting of AKI and the change in biomarker values serve as secondary end points in therapeutic trials to improve outcomes (50). Thus, biomarkers will remain an extremely active area of clinical investigation and continue to inform and refine our understanding of AKI. Large multicenter investigations of biomarkers will advance the field of AKI and work to improve patient outcomes in the setting of renal injury.

Disclosures

C.R.P. is a named coinventor on the IL-18 patent (no commercial value) issued to University of Colorado.

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