Biomarkers of Acute Kidney Injury

By Suneel M. Udani and Jay L. Koyner

Over the past decade there has been an explosion of research investigating biomarkers of acute kidney injury (AKI). The research was borne out of the desire to replace serum creatinine, and in part urine output, as for a variety of reasons both serve as suboptimal tools in the diagnosis of acute renal tubular injury. The biomarker movement has been assisted by internationally accepted, standardized, consensus definitions of AKI. Whereas decades ago AKI definitions varied from study to study, the implementation and validation of the RIFLE (Risk, Injury, Failure, Loss and End Stage) and AKI Network criteria paved the way for the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (1). In solidifying the definition of AKI these criteria have helped to quantify the growing number of AKI cases, facilitated the growth of the biomarker field, as well as allowed for the comparison of biomarkers and event rates across studies.

While initial investigations into several modern biomarkers of AKI demonstrated remarkable promise in the ability to detect AKI earlier than serum creatinine, subsequent attempts to validate these smaller studies in large-scale multicenter trials have failed to match the original success. Perhaps most importantly the intense investigation of biomarkers has demonstrated that AKI is a complex clinical syndrome that is often the result of multiple renal insults. For example, while AKI following cardiac surgery has traditionally been thought to be related to ischemic injury, in fact there are multiple factors that can impact the development and outcome of cardiac surgery-associated AKI, including ischemic injury; inflammatory response from, and duration of, cardiopulmonary bypass; need for peroperative mechanical ventilation; need for intra- and peroperative blood products; and preoperative comorbidities (most importantly CKD) amongst others. As nephrologists, we see AKI associated with a variety of clinical settings/factors including cardiac surgery, sepsis, nephrotoxins, and trauma. However comingling of these settings/issues in individual patients is extremely common, and as such it is unrealistic to expect one marker (known to be upregulated due to inflammation or ischemia or some other injurious event) to be able to diagnose early AKI in all of these settings.

Research into the field of AKI biomarkers first set out to find the “renal troponin,” which detects injury earlier than serum creatinine/urine output, and over the past several years countless studies have demonstrated that several modern biomarkers can do this. Whether it is data from the Endre and colleagues (2) from the EARLY ARF trial (investigating AKI in mixed medical-surgical intensive care units [ICUs]) or those from Parikh and colleagues from the TRIBE AKI (3,4) study (investigating AKI after adult and pediatric cardiac surgery) several biomarkers have been shown to detect AKI earlier than changes in serum creatinine. In these and other studies, many biomarkers (e.g., plasma and urine neutrophil gelatinase-associated lipocalin [NGAL], urine interleukin-18 [IL-18], or urinary kidney injury molecule-1 [KIM-1]) demonstrated mild to moderate success in predicting early AKI (areas under the curve [AUCs] of 0.60 to 0.80). However, given these results, some in the field have shifted their focus towards enhancing the AKI diagnostic capabilities via the utilization of modern biomarkers of AKI in conjunction with serum creatinine.

This idea has gained traction over the last 2 to 3 years with multiple groups demonstrating diagnostic and prognostic improvements when using modern biomarkers of AKI in conjunction with changes in serum creatinine. Utilizing biomarkers in the setting of small increases in serum creatinine or drops in urine output (e.g., KDIGO Stage 1 AKI) has been demonstrated to be effective in detecting those patients who will go on to develop more severe AKI (e.g., KDIGO Stage 3) or the future need for renal replacement therapy. In fact, a variety of biomarkers—including plasma NGAL, urinary albumin to creatinine ratio, urine IL-18, and the product of urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metallocproteinases-2 (TIMP-2)—have all been shown to reliably forecast the future development of severe AKI when measured following adult cardiac surgery or early in the course of ICU admission/critical illness (5,6). Of note, besides modern biomarkers, recent data demonstrates that urine output in the 2 hours following a standardized high-dose furosemide challenge in euvalmic patients with early AKI also reliably forecasts progression to stage 3 AKI (7).

In addition to being used in the ICU in conjunction with serum creatinine, several recent studies have demonstrated that modern biomarkers can detect those patients at greatest risk for inpatient AKI at the time of emergency room (ER) arrival. Urine NGAL, serum cystatin C, and others have been shown to predict which patients will go on to develop AKI during their hospital stay (8,9). Perhaps more importantly, several of the ER studies have demonstrated that modern biomarkers can aid in distinguishing those with volume-responsive AKI from those with intrinsic renal tubular damage/acute tubular necrosis. This ability to distinguish those with a change in glomerular filtration/function but no change in tubular function (traditionally thought of a “prenatal azotemia”) from those with both a change in function and tubular damage is exactly what nephrologists have been looking for over the last several decades. Separately, in 2012 Dui et al. (10) and Nejat et al. (11) published data in Kidney International that demonstrated several modern biomarkers (including NGAL, KIM-1, and urine Liver Fatty Acid Binding Protein [LFABP]) all had the ability to differentiate transient and sustained-intrinsic AKI in critically ill ICU patients. This ability to separate out those with transient reversible AKI from those with intrinsic tubular injury and acute tubular necrosis will be invaluable as nephrologists embark on clinical trials to treat and/or prevent AKI. In an attempt to maximize clinical trial funding, AKI investigators should attempt to enroll patients who will meet hard end points like KDIGO Stage 3. The need for renal replacement therapy and mortality will be of the utmost importance in order to maximize clinical trial funding. Table 1 summarizes the findings of several studies investigating modern biomarkers of AKI in a variety of clinical settings for several clinical end points.

Despite these data and their promise, modern biomarkers continue to have several limitations. First, biomarker performance has been measured against serum creatinine, which is not exactly a true gold standard. Second, as of March 2014, the U.S. Food and Drug Administration has not approved any of these biomarker assays for clinical use. In fact, several of the biomarkers have multiple commercially available research assays.

Table 1. Biomarker performance in detecting AKI in a variety of clinical settings

<table>
<thead>
<tr>
<th>Type of AKI</th>
<th>Perioperative AKI</th>
<th>Critically Ill</th>
<th>Emergency Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Post-op AKI</td>
<td>AKI progression</td>
<td>Long-Term Mortality</td>
<td>Early Diagnosis of AKI</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blood NGAL</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Blood CysC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine IL-18</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine LFABP</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TIMP-2/IGFBP7</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine Protein/Albumin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*AKI = acute kidney injury; CysC = cystatin C; IGFBP7 = insulin-like growth factor-binding protein 7; IL-18 = interleukin 18; KIM-1 = kidney injury molecule-1; LFABP = liver fatty acid binding protein; NGAL = neutrophil gelatinase associated lipocalin; op = operative; RRT = renal replacement therapy; TIMP-2 = tissue inhibitor of metallocproteinases-2; + = 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. Adapted and expanded from Koyner JL, Parikh CR. Clin J Am Soc Nephrol 2013; 8:1034–1042.
which only serve to confound the published literature. Finally, the ability to combine biomarkers to augment their diagnostic and prognostic performance remains statistically problematic.

In summary, there are several viable modern biomarkers of AKI. Each biomarker has its own individual profile, with some excelling at identifying early AKI while other can provide insight into the differential diagnosis of AKI (transient vs. intrinsic AKI). Over the next few years, undoubtedly new biomarkers will be discovered and established ones will be further validated. Eventually, biomarkers will be used as triggers for therapeutic AKI interventions or to risk-stratify patients to determine who would benefit from the early initiation of renal replacement therapy. Over the last decade nephrologists have laid the foundation for the next decade, which will see a shift towards these assays being used for clinical care while still being utilized in AKI research.

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References