



American Society of Nephrology
1401 H St NW, Suite 900
Washington, DC 20005
Phone: 202-640-4660 | Fax 202-637-9793
vramsey@kidney360.org

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Rolando Claire-Del Granado, Etienne Macedo, and Jonathan Chávez-Íñiguez

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Biomarkers for Early Diagnosis of AKI: Could it backfire?

Rolando Claure-Del Granado^{1,2}; Etienne Macedo³; and Jonathan S. Chávez-Íñiguez^{4,5}

¹Division of Nephrology Hospital Obrero No 2 – CNS; Cochabamba, Bolivia. ²IIBISMED, Universidad Mayor de San Simon, School of Medicine; Cochabamba, Bolivia. ³Division of Nephrology-Hypertension University of California San Diego; California, USA.

⁴Division of Nephrology Hospital Civil de Guadalajara “Fray Antonio Alcalde”; Guadalajara, Jalisco, Mexico. ⁵University of Guadalajara Health Sciences Center; Guadalajara, Jalisco, Mexico.

Corresponding author

Rolando Claure-Del Granado, MD, FASN

Division of Nephrology

Hospital Obrero No 2 – CNS

Cochabamba, Bolivia

Phone: +591 759-08833

Email: rclaure@yahoo.com

The term acute kidney injury (AKI) has considerably evolved since its development almost 60 years in 1964; AKI has gone through more than 30 definitions that have considered serum creatinine (sCr) and occasionally urine output. A rise in sCr value is an excellent biomarker to identify late changes in kidney function but not to detect an early injury or to identify structural damage (subclinical AKI). We know the strengths and weaknesses of sCr; it is the "Janus faces" for nephrologists when talking about AKI, hated and loved for decades. However, despite many weaknesses as a biomarker, it is still the most used test to identify kidney injury globally; it is inexpensive, available in most places, and a known marker of kidney injury not only by nephrologists but also by other health care professionals. It is unlikely that we will stop using sCr in the upcoming years(1).

For this reason, the use of novel biomarkers was proposed to improve the timely detection of early AKI, improve the differential diagnosis and prognostic assessment, to provide early interventions and improve its management. Different biomarkers with greater sensitivity and specificity have been discovered, including proteomics, which identifies changes in the metabolism of different zones of the nephron earlier in the event of a kidney insult; such biomarkers have been a subject of intense ongoing interest (Table).

These novel biomarkers of structural AKI (subclinical AKI) were expected to provide critical diagnostic and prognostic stratification and complement sCr and urine output as proposed recently by the 10th Acute Disease Quality Initiative (ADQI) consensus meeting (2). While several of these novel biomarkers have been assessed in diverse populations and various clinical scenarios, their implementation in routine clinical practice has not been embraced. Comparison to an imperfect gold standard (sCr), the unclear impact of chronic kidney disease on biomarker performance, and the use in different pathophysiological disease processes (nephrotoxins, hemodynamic, sepsis-associated AKI, etc.) have delayed their use in clinical practice(3-5). Another important aspect that must be considered is that most novel AKI biomarkers studied so far have been measured in urine. Measuring biomarkers in the urine have some advantages, including being non-invasive, the reduced number of interfering proteins, and the

increased specificity for kidney injury. However, disadvantages include the lack of samples from patients with severe oliguria and potential changes in urinary biomarker concentrations induced by the hydration status and diuretic therapy(6). A commonly employed correction factor for urinary dilution is to express urinary biomarkers adjusted for urinary creatinine concentration in research studies. However, this correction may be inaccurate in the situation of AKI as creatinine production may be reduced in some forms of AKI, and both plasma and urine creatinine kinetics are significantly altered in the early phases of AKI(7). Although timed urine collection is a more accurate method to assess urinary biomarkers, in the acute care settings this is usually difficult. Indexing or adjusting spot urinary biomarker concentrations for urine creatinine concentration would not alter their prognostication of outcomes but more studies are needed(8).

One of the great problems with biomarkers has been their indiscriminate use to study different types of AKI. We know that AKI is a heterogeneous syndrome with different presentations and does not usually follow a specific pattern. Its phenotype changes according to diverse etiologies and comorbidities; therefore, it is unlikely that a single biomarker will capture all clinical scenarios of AKI. It is more likely that a more complex, multicomponent predictive biomarker system will be required to implement biomarkers in routine clinical practice successfully. Ideally, these biomarkers would be able to detail the severity of AKI, the likelihood of AKI progressing to more severe stages or the need for KRT, the likelihood of renal recovery and overall prognosis(9).

Biomarkers may pinpoint the site or mechanism of injury and in doing so may lead to targeted pharmacotherapy(10). The discovery of specific biomarkers of kidney tubular and glomerular function may help better understand the pathophysiological process and determine the component and location of the injury. Based on this assumption, pairing biomarkers that identify different sites of injury or dysfunction can be useful in clinical practice. A great example is pairing of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) which together improved the area under the curve (AUC) for the detection of AKI over single biomarkers. Other examples exist such as the combined use of interleukin-18 and

kidney injury molecule 1 (KIM-1). A recent study in 32 patients with established acute interstitial nephritis (AIN) by kidney biopsy reviewed by three pathologists independently, showed that Urine TNF- α and IL-9 were consistently higher in AIN patients as compared to those with other diagnoses, including acute tubular injury, glomerular diseases, and diabetic kidney disease, and those without any kidney disease(11). The combination of biomarkers, even after controlling for blood eosinophils, leukocyturia, and proteinuria improved over clinicians' prebiopsy diagnosis. In drug-induced interstitial nephritis (DTIN), a combination of urinary biomarkers correlated and was predictive of the gradated severity of acute lesions in DTIN(12).

As we have mentioned previously, the holy grail of biomarkers would be their use for improving our management leading to change the clinical course of AKI and better outcomes. Unfortunately, there is still a lack of consistent evidence to show that they can be used in the therapeutic decision-making process. In different cohorts, the use of biomarkers to guide AKI treatment has been tested with controversial results. For example, significant effort have been made to incorporate NGAL in the kidney replacement therapy (KRT) decision-making process. The early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury ELAIN study, where patients with stage 2 AKI were included, were randomized to early versus the delayed start of KRT, excluding patients with plasmatic NGAL <150 ng/dL. The authors tried to select cases with a higher probability of having severe AKI avoiding treating patients with KRT who may otherwise spontaneously recovered kidney function; it is worth mentioning that most patients had values >400 ng/dL(13). In a recent systematic review and meta-analysis including all trials evaluating biomarker performance for the prediction of KRT in AKI, the pooled AUCs (95% CI) for urine and blood NGAL were 0.720 (0.638-0.803) and 0.755 (0.706-0.803), respectively(14). Some biomarkers have reasonable potential to aid clinical decision-making regarding when to start KRT in AKI. However, we consider that the current strength of evidence would essentially preclude their routine use pending further validation studies. Implementation studies using biomarkers to identify high-risk patients have been published recently. In the PrevAKI trial the authors examined the feasibility of

implementing the KDIGO bundle of care in high-risk patients undergoing cardiac surgery identified by urinary biomarkers (NephroCheck®). The occurrence of moderate and severe AKI was significantly lower in the intervention group as compared to the control group (14.0% vs 23.9%; absolute risk reduction of 10.0% (95% CI, 0.9-19.1); $p = .034$)(15). In the pediatric population, the Nephrotoxic Injury Negated by Just-in time Action (NINJA) program is a good example of the use of biomarkers to identify high-risk populations coupled with a systematic approach that could improve AKI care. In this study, investigators observed a significant and sustained 23.8% decrease in nephrotoxic medication-associated AKI(16). Another clinical trial attempted to identify patients with a high risk of kidney-related complications in the emergency room using NephroCheck® values >0.3 ($(\text{TIMP-2}) \times (\text{IGFBP7})$) to evaluate if early treatment prevented the progression and severity of AKI. Patients were randomized either to nephrology guided early intervention that consisted: of corrections of glucose values, withdrawal of nephrotoxic drugs, hemodynamic and fluid optimization, or standard care (without nephrology intervention); unfortunately, the frequency of patients developing AKI was similar in both groups, despite early nephrology intervention(17).

The combination of novel biomarkers with instruments designed for predicting persistent or for detection of severe AKI like the renal angina index (RAI) could improve the performance of this instrument as shown by Matsuura et al. a combination of the RAI and urinary L-FABP also contributed greatly to stratifying higher risk patients with severe AKI(18). Finally, novel biomarkers have been evaluated to enable prediction of persistence of renal dysfunction and renal non-recovery. In the RUBY study, the urinary C-C motif chemokine ligand 14 (CCL14) was identified with the most predictive capacity of persistent stage 3 AKI with an AUC (95% CI) of 0.83 (0.78-0.87)(19).

Currently, the only FDA approved biomarker is the NephroCheck®, which is not available in several places and its cost is not affordable in low-middle income countries. In high income countries like the United States, coverage policy differences across insurance health plans have limited the accessibility to their use and patients may incur burdensome out-of-pocket costs depending on their insurance plan

benefits. This inequality may also create barriers to testing and contribute to health disparities. The variable cutoff values in published articles, risk of confounding by comorbidities, lack of standardization, availability and high expenses are important barriers to access and sustainability of AKI biomarker implementation. These issues could explain why in an international survey of AKI management 40% of nephrologists and intensivists have used novel biomarkers in routine clinical practice and only 23% used them for research purposes (20).

The synergistic role of biomarkers should be coupled with standard clinical parameters to improve the outcome for AKI patients(21). The main goal of novel biomarkers are not to replace clinical judgment or older markers but instead to add prediction value when applied together. Recently, urine neutrophil gelatinase-associated lipocalin (uNGAL) and SCr samples from ICU admission were studied in 178 children. Patients with uNGAL+/SCr-, had increased almost 4-fold increased risk for all-stage Day 3 AKI (\geq KDIGO stage 1) compared to those with uNGAL-/SCr-. Compared to uNGAL-/SCr+, patients uNGAL+/SCr+ had 12-fold increased risk for severe day 3 AKI (\geq KDIGO stage 2). The only patients to suffer all-stage day 3 AKI and mortality were uNGAL+ (3.2% uNGAL+/SCr-; 6.5% uNGAL+/SCr+)(22).

Establishing this multicomponent biomarker for a given clinical scenario will still require prospective validation in large cohorts including patients with a diverse AKI causes. In order to have a clinically useful predictive power through a multicomponent marker, it is likely that we will need first to decrease cost and expand the use of the available markers.

We believe that biomarkers could improve care in AKI and despite their limitations and barriers to their clinical use, biomarkers will permit assessment of renal stress or injury before permanent damage occurs, allowing the implementation of a combination of therapies that may reverse the course or blunt the severity of kidney injury (Figure)(23, 24). The association of early elevation of biomarkers with clinically meaningful outcomes such as early AKI, progression of AKI, and need for KRT is clear; and their application can potentially help to stratify patients with different pathophysiology and guide us on more appropriate and individualized therapies(25).

Disclosures

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Author Contributions

Rolando Claire-Del Granado: Conceptualization; Writing - original draft; Writing - review and editing.

Etienne Macedo: Writing - original draft.

Jonathan Chávez-Íñiguez: Writing - original draft; Writing - review and editing.

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Table. Serum creatinine, biomarkers and its relationship between different AKI scenarios

AKI scenarios	SERUM CREATININE	BIOMARKER	EXAMPLE
Kidney stress	✓	✓	Cr: identifies patients with mild CKD who are most at risk for developing AKI Biom: revealed when at risk of AKI
Subclinical AKI	✗	✓	Cr: after the insult it takes up to 48 hours to rise Biom: some rises in the first hours
AKI diagnosis	✓	✗	Cr: the diagnosis of AKI by KDIGO is made by an increase in serum creatinine and a decrease in urinary output Biom: the ADQI group proposes to add biomarkers to the classification, not yet incorporated into KDIGO guideline
Prediction of severe AKI (2,3)	✗	✓	Cr: does not identify which patient progressed to severe AKI Biom: Nephrochek >0.3 and NGAL >450 ng/mL predicts AKI severity
Start KRT	✗	✗	Cr: does not identify which patient should start KRT Biom: does not identify which patient should start KRT
Stop KRT	✗	✗	Cr: does not identify when to stop KRT Biom: does not identify when to stop KRT
Acute tubular necrosis	✗	✗	Cr: does not identify histology with ATN Biom: does not identify histology with ATN
Acute interstitial nephritis	✗	✓	Cr: does not identify histology with AIN Biom: high values of TNF- α and IL-9 may identify AIN
Contrast associated nephropathy	✓	✓	Cr: increases 12 hours after contrast application Biom: Cystatin C rises earlier and is more sensitive than creatinine
Sepsis associated AKI	✗	✓	Cr: low the synthesis during sepsis Biom: NGAL could have better performance identifying AKI than creatinine
Proximal tubular damage	✗	✓	Cr: does not identify proximal tubular damage Biom: Cystatin C, IL-18, NGAL, L-FABP, could identify proximal tubular

			damage
Kidney function improvement after AKI	✗	✓	Cr: does not identify renal repair or improvement Biom: KIM-1, NGAL, Nephrocheck have been shown to be associated with kidney improvement or repair
AKD or CKD progression from AKI	✓	✓	Cr: creatinine values have been associated with progression to AKD and CKD Biom: KIM-1, Angt, NGAL, Nephrocheck have been associated with progression to CKD
Guide therapy	✗	✗	Cr: its values do not guide management or treatment Biom: there is still not enough evidence to guide management or treatment due to its elevation
Availability	✓	✗	Cr: universal availability and wide acceptance by health personnel Biom: not available in many places, low acceptance by health personnel
Cost	✓	✗	Cr: cheap and affordable Biom: expensive

AIN, acute interstitial nephritis; AKD, acute kidney disease; AKI, acute kidney injury; Ang, angiotensin; ATN, acute tubular necrosis; Biom, biomarker; CKD, chronic kidney disease; Cr, creatinine; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; KRT, kidney replacement therapy; L-FABP, Liver-Type Fatty Acid–Binding Protein; N-GAL, neutrophil gelatinase-associated lipocalin

Figure Legend.

Biomarker competition for finding an ideal biomarker for improving early detection, management and outcomes of AKI and barriers for their implementation.

Figure 1

