Kidney Disease Complexity Manifested: One Biomarker Size Does Not Fit All

Mythri Shankar¹ and Stuart L. Goldstein²

¹Department of Internal Medicine, Institute of Nephro-Urology, Bengaluru, India; and ²Division of Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA

Kidney Int Rep (2022) 7, 1458–1460; https://doi.org/10.1016/j.ekir.2022.05.037 © 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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A biomarker is a specific measurable biological indicator that will assess the risk, presence, or stage of a disease. Biomarkers can be used for screening, diagnoses, and monitoring disease activity. The National Institutes of Health Biomarkers Definitions Working Group defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological pro-cesses, pathogenic processes, or pharmaco-logic responses to a therapeutic intervention.” An ideal biomarker should be noninvasive, highly sensitive and specific, easily measurable, biologically plausible, inexpensive, and vary with disease severity and treatment.

Conventional kidney function biomarkers include serum creatinine, urine microscopy, and urine output. Acute kidney injury (AKI) is defined by a rise in serum creatinine or a decrease in urine output, which can be reflective as a decrease in glomerular filtration rate changes and is a suboptimal biomarker. It has poor sensitivity for AKI and does not help in differentiating between various causes of AKI. By the time serum creatinine levels rise, a crucial therapeutic window may be missed, especially in cases of acute tubular injury. Other reasons for the slow increase in creatinine values may be the dilutional effect of i.v. fluids and decreased creatinine production. Therefore, various urine and serum biomarkers have been assessed for more timely diagnosis and differentiation of structural versus functional AKI over the past 2 decades (Table 1).

The association between AKI severity and subsequent development of chronic kidney disease (CKD) has been described extensively over the past 2 decades. Whether this relationship is causal or not is a matter of debate, yet it is important to follow up with some patients who survive an episode of AKI for development of CKD because such surveillance has the potential to improve patient outcomes. Accurate prediction of patients who are truly at risk of developing CKD after AKI has been elusive, and current best practice still requires functional monitoring after hospitalization. Thus, if tubular AKI biomarker concentration trajectories or levels delineate patients at risk for CKD earlier than waiting for functional change at 3 or 6 months, resources would be focused efficiently for follow-up.

In this context, Wen et al. leveraged the Assessment, Serial Evaluation, and Subsequent Sequelae of AKI (ASSESS-AKI) study cardiac surgery cohort to evaluate potential biomarker associations with CKD after an episode of AKI in this issue of Kidney Reports. Half of the 1538 ASSESS-AKI cohort subjects developed in-hospital AKI after cardiac surgery, and 300 (20%) of them developed CKD. Most urinary biomarkers are measured from spot urine samples and therefore can be indexed to urine creatinine concentration or osmolarity. This methodology considers the variation of urine concentration to estimate a rate of biomarker excretion. However, urine creatinine concentration varies widely and depends on individual characteristics such as sex, diet, muscle mass, and function of the proximal tubule. Thus, whereas it is common to index clinically available urine analyte (e.g., microalbumin, protein, and calcium) concentrations to creatinine, the authors also tested the hypothesis that indexing would strengthen individual AKI biomarker associations with CKD.

The authors observed variable effects of indexing on CKD prediction. Interestingly, in-hospital urine creatinine concentration and osmolarity were both inversely associated with CKD development at 3 months. This inverse relationship suggests that tubular function preservation may be a protective predictor of lack of CKD development. These relationships were not maintained 3 months after the AKI episode. Indexing urine KIM-1, IL-18, and MCP-1 to urine creatinine or urine

Correspondence: Stuart L. Goldstein, Division of Nephrology and Hypertension, Cincinnati Children Hospital, 3333 Burnet Avenue, MLC 7022, Cincinnati, Ohio 45229, USA. E-mail: stuart.goldstein@cchmc.org

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Table 1. Biomarkers of acute kidney injury

| Biomarkers                                      | Source                                                                 | Clinical significance                                                                 | Validation                                                                                     | Time of detection                                                                 | References                |
|------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------|
| Urinary tubular enzymes.                       | Enzymes Released from damaged tubular epithelial cells                | Elevated in AKI and acute tubular necrosis                                             | Further validation is needed to differentiate between prerenal AKI and ATN                   | It is released within 12 hours of injury and is seen 4 days before the elevation of serum creatinine | Lisowska-Myjak et al.    |
| Proximal renal tubular epithelial antigen (HRTE-1), α-glutathione S-transferase, pi-glutathione S-transferase, gamma-glutamyltranspeptidase, alanine aminopeptidase, lactate dehydrogenase, N-acetyl-β-glucosaminidase, and alkaline phosphatase |                                                                         |                                                                                        |                                                                                           |                                                                          |                          |
| Urinary low-molecular-weight proteins           | α1-microglobulin, β2-microglobulin, retinol-binding protein, adenosine |                                                                                       |                                                                                               |                                                                                           | Herget-Rosenthal et al.   |
| Neutrophil gelatinase-associated lipocatin      | Is predominantly produced by thick ascending limb of the loop of Henle and intercalated cells of the collecting duct | Ischemic, septic, post-transplantation AKI, decompensated cirrhosis, type 1 cardioenal syndrome | May be useful for early injury prediction and progression of injury. Can differentiate between ATN vs. prerenal AKI. Approved as biomarker of AKI in some countries | Can be detected 3 hours after injury, peaks in 8–12 hours, persists for 5 days | Albert et al.             |
| Urinary kidney injury molecule-1                | Produced predominately by proximal tubular epithelial cells in ischemic and toxic injury | Elevated levels correlated with increased risk in death or hospitalization in cardiac studies | Further validation is needed                                                                 | Detected as early as 24 hours after tubular injury                                        | Ghatanatti et al.         |
| T cell immunoglobulin mucin domain-1            |                                                                         |                                                                                       |                                                                                               |                                                                                           |                          |
| Urinary interleukin-18                         | Formed in the proximal tubules                                         | Biomarker of renal parenhyal injury. Elevated in ATN compared with prerenal AKI, urinary tract infection, or CKD | Further validation is needed                                                                 | Peaks around 12 hours of injury                                                            | Parikh et al.             |
| Urinary liver-type fatty acid-binding protein   | Secreted by proximal tubular epithelial cells during ischemic and hypoxic injury | Correlates strongly with ischemic time in post-transplant patients, elevated after cardiac surgery, a predictor of poor prognosis | Further validation is needed                                                                 |                                                                                           | Yamamoto et al.           |
| Urinary angiotensinogen                         |                                                                        | It is promising to detect progressive AKI, especially in acute decompensated heart failure | Further validation needed                                                                  |                                                                                           | Chen et al.               |
| Urinary Calprotectin                            |                                                                        | Promising role in differentiating ATN vs. prerenal AKI                                 | Further validation neededIt is secreted by immune cells as danger-associated molecular pattern protein | Detected within 2 hours and peaked by 48 hrs                                              | Chen et al.               |
| Urinary TIMP-2 × IGFBP-7 (Commercially marketed as NephroCheck) |                                                                        | Predicts AKI in critically ill and perioperative patients                              | It is approved by US FDA                                                                   | Detected in the urine within 4 hours whereas serum creatinine took 1 to 3 days to increase | Timi et al.               |

AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; FDA, Food and Drug Administration.
osmolarity strengthened their association and prediction of CKD, whereas the same was not observed for urine albumin, NGAL or YKL-40. Furthermore, indexing uromodulin, an AKI biomarker that is lower in patients who do not develop AKI, resulted in a diminution of its negative predictive performance. As a result, the authors provide helpful clinical recommendation scenarios in Figure 2 of their manuscript to guide indexing biomarkers to urine creatinine or osmolarity.

The authors’ work and findings are important and have both clinical and research implications for the AKI field. The ASSESS-AKI parent study was well-designed and rigorously executed with a large patient sample size, and AKI rates are consistent with other published cardiac surgery associated AKI epidemiologic studies. With respect to future AKI biomarker research, the current work provides cautionary advice to ensure that studies evaluating certain biomarkers (e.g., KIM-1, IL-18, MCP-1) index and adjust for urine creatinine and osmolarity. More importantly, when “more” novel biomarkers undergo evaluation in the future, the authors make a strong case for indexing as well.

The clinical implications are currently less pressing or evident. Only 2 AKI biomarkers, TIMP-2*IGBP7 and NGAL are widely available in clinical practice, and only the former has been approved by the US Food and Drug Administration (Nephrocheck, Biomerieux Inc.). Neither of these biomarkers have been studied extensively to predict CKD, and NGAL is generally not elevated in patients who develop CKD after AKI at the time of CKD diagnosis.s15

Evidently, more work is needed to translate this important work for clinical purposes. Several studies have assessed different biomarkers for CKD, albeit mostly in diabetic kidney disease (Supplementary Table S1). In the current issue, Amatruda et al.5 studied 6 urinary biomarkers specific to kidney tubule health in diabetic kidney disease for patients with an estimated glomerular filtration rate of <60 ml/min per 1.73 m². These were as follows: KIM-1 (tubule injury), MCP-1 (interstitial fibrosis), YKL-40 (tubule epithelial repair), α1-microglobulin (proximal tubule resorptive capacity), UMOD, and epidermal growth factor (synthetic function of the tubule). They observed that higher urine KIM-1, α1-microglobulin, and MCP-1 were independently associated with disease progression to end-stage kidney disease. These important findings highlight the potential mechanism of rapid CKD progression and therefore, potential therapeutic targets.

A takeaway message from these 2 complementary studies is that acute kidney disease and CKD, while connected, have different mechanistic underpinnings which are manifested by different biomarker patterns and even the way the biomarker is assessed. The complexity of both AKI and CKD is repeatedly demonstrated in the literature. These 2 studies continue the long research journey to provide clinicians with tools to help identify who is at risk for CKD development and progression.

DISCLOSURE
SLG is a consultant for and receives grant funding from Bioponto, Inc. MS declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary References.
Table S1. Biomarkers of chronic kidney disease.

REFERENCES
1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95. https://doi.org/10.1067/mcp.2001.113989
2. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group - KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;2:124–138.
3. Bonventre JV. Diagnosis of acute kidney injury: from classic parameters to new biomarkers. Contrib Nephrol. 2007;156:213–219. https://doi.org/10.1159/000010286
4. Pickering JW, Ralib AM, Endre ZH. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. Crit Care. 2013;17:R7. https://doi.org/10.1186/cc11931
5. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med. 2011;39:2665–2671. https://doi.org/10.1097/CCM.0b013e318228234b
6. Endre ZH, Kellum JA, Di Somma S, et al. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. Contrib Nephrol. 2013;182:30–44. https://doi.org/10.1159/000349964
7. Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open. 2020;3:e2019209. https://doi.org/10.1001/jamanetworkopen.2020.19209
8. Wen Y, Thiessen-Philbrook H, Moledina DG, et al. Considerations in controlling for urine concentration for biomarkers of kidney disease progression after acute kidney injury. Kidney Int Rep. 2022;7:1502–1513. https://doi.org/10.1016/j.ekir.2022.03.026
9. Amatruda JG, Katz R, Sarnak MJ, et al. Biomarkers of kidney tubule disease and risk of end-stage kidney disease in persons with diabetes and CKD. Kidney Int Rep. 2022;7:1514–1523. https://doi.org/10.1016/j.ekir.2022.03.033

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