THE ROLE OF BIOMARKERS IN ACUTE KIDNEY INJURY

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INTRODUCTION TO AKI AND AKI BIOMARKERS

Diagnosis of acute kidney injury (AKI) usually comes late, from the actual insult to the kidneys to changes in creatinine and/or urine output. The main advantage of using new biomarkers is making earlier diagnosis, management and prognostication of AKI possible even before changes in creatinine and/or urine output take place. However, not all of these biomarkers are well-validated and have a protocol for guiding application in clinical settings. In this section, we will define what AKI is, its classification and what are its common causes. We will also enumerate here common biomarkers of AKI and their potential role in clinical practice.

WHAT'S NEW ON AKI BIOMARKERS?

In this section, we will bring you some late developments on AKI biomarkers. First, the use of two FDA–approved cell cycle arrest biomarkers to improve grading in AKI. Second, how levels of metals in urine can serve as early biomarkers for AKI. Third would be the role of endotrophin in predicting outcomes after AKI. Fourth will be the use of a combination of injury biomarkers with functional markers to aid in prognostication in AKI. We will close the issue with a commentary on how far along are we in the clinics with the use of biomarkers for AKI.

DISCLOSURE:

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FRESENIUS MEDICAL CARE

INTRODUCTION TO AKI AND AKI BIOMARKERS

KDIGO defines acute kidney injury (AKI) as any of the following: (1) increase in serum creatinine by 0.3 mg/dL or more within 48 hours or (2) increase in serum creatinine to 1.5 times baseline or more within the last 7 days or (3) urine output less than 0.5 mL/kg/h for 6 hours. KDIGO also recommended a staging system to rate the severity of AKI (Table 1). [1] Earlier classification systems for AKI include the RIFLE and AKIN and are not recommended to be used in practice anymore. [2,3,4] Causes of AKI are classified either as (1) pre-renal (e.g. bleeding, dehydration, renal vascular disease and heart failure) (2) renal (e.g. glomerulonephritis, sepsis and autoimmune diseases such as SLE) or (3) post-renal causes (e.g. obstruction of urinary tract with stones or malignant tissues). [5,6,7]

The Acute Disease Quality Initiative (ADQI) Consensus Conference stated that biomarkers for AKI serve different purposes in the clinics and may be used either for risk assessment, prediction of severity of AKI, and to assess AKI progression and kidney recovery. A few examples are presented here. (Table 2) [8]

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline or ≥0.3 mg/dL increase	< 0.5 mL/kg/h for 6 h
2	2-2.9 times baseline	< 0.5 mL/kg/h for 12 h
3	3 times baseline or Increase in serum creatinine to ≥4 mg/dL or Initiation of kidney replacement therapy	< 0.3 mL/kg/h for 24 h or anuria for ≥12 h

Table 1. KDIGO Staging for AKI Severity. Adapted from Kidney Int Suppl. 2012; 2: 1–138.

AKI biomarker	Sampling	Potential Role in Clinical Practice				
		Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Dickkopf-3	Urine	✓	✓			
Tissue metalloproteinase-2; insulin-like growth factor binding protein-7	Urine		✓	✓	✓	
Hepatocyte growth factor	Plasma				✓	✓
Hepcidin	Urine and plasma			✓	✓	
Interleukin-18	Urine		✓	✓		
Kidney injury molecule–1	Urine		✓	✓	✓	
Micro-RNA	Urine and plasma			✓		
Neutrophil gelatinase-associated Lipocalin (NGAL)	Urine and plasma			✓	✓	
Osteopontin	Plasma			✓	✓	
Proenkephalin A	Plasma			✓	✓	✓
Tumor necrosis factor	Plasma			✓		

Table 2. Common AKI Biomarkers and Roles in Clinical Practice. Adapted from JAMA Network Open. 2020;3(10):e2019209.

WHAT'S NEW ON AKI BIOMARKERS?

The presence of two cell-cycle arrest urinary biomarkers, **tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin like growth factor binding protein 7 (IGFBP7)**, was shown to refine the KDIGO AKI grading system, according to a study conducted using data from the ProCESS trial (N=900 patients in various KDIGO AKI stages [Stage 1,2,3–15.2%, 29.4%, and 18% respectively]). Patients who were positive with these two **FDA approved biomarkers** vs. biomarker-negative patients with KDIGO AKI stage 1, 2, and 3 had 2.2-, 1.5-, and 1.6-fold higher risk for mortality within 30 days. [9,10] Another study that used TIMP-2 and IGFBP7 cut-off values for management of cardiac patients at risk for AKI demonstrated significant reduction of AKI and improved hemodynamic parameters vs. controls. [11] The ADQI also recommends further subcategorization of KDIGO AKI stages 1 (1S, 1A, 1B), 2 (2A, 2B) and 3 (3A, 3B) using other biomarkers apart from TIMP-2 and IGFBP7, including urine NGAL and serum creatinine. [8]

A recent report has demonstrated that **urinary cadmium (Cd), copper (Cu) and zinc (Zn)** may be utilized as cost-effective biomarkers for early detection of AKI. The study is performed on porcine ischemic AKI models to identify urine trace element biomarkers. Cardiac surgery (N=151) and ICU patients (N=150) were then recruited from a single center in the UK to test the applicability of the three metals as AKI biomarkers. Results from the analysis showed that urinary Cd, Cu, and Zn can be used as novel biomarkers for early detection of AKI. Urinary trace metals have advantages over proteins as AKI biomarkers because they are stable at room temperature and have potential for use in point-of-care (POC) testing. [12]

Investigators from Denmark and the UK showed in the AKI Risk in Derby (ARID) study (N=393) that **endotrophin (ETP)** levels, a molecule released during formation of collagen type VI, were significantly higher in AKI patients vs. controls. ETP was shown to discriminate patients with kidney progression at year 3 (area under the curve, AUC=0.67, p=0.01) and could also discriminate survivors vs. non-survivors at year 3 (AUC=0.64, p<0.01) hence its possible clinical utility in predicting disease progression and mortality. [13]

A study from experts from the University of Cincinnati, US in a prospective observational study among over 200 pediatric ICU patients showed that the Renal Angina Index (RAI) with the use of NGAL and serum creatinine may improve prognostication in AKI. RAI+ subjects 12 hours post-admission who were NGAL+ demonstrated higher risk of Day 3 AKI, kidney replacement therapy use, and mortality. [14]

EXPERT COMMENTARY (with Dr Michael Etter, Senior VP, Global Chief Medical Officer, AP)
How far along are we with the use of AKI biomarkers in the clinics? What promise do these biomarkers hold in terms of patient management?

The identification of the ideal AKI biomarker would potentially have significant impact on clinical practice and patient outcomes. There are many promising approaches but due to the heterogeneity of AKI in terms of causal mechanism and prognosis, the limitations of a single biomarker and long roads to the validation of candidates, we are still quite some distance away for this goal.

We have seen candidates like urine NGAL that has been around for more than 15 years but failed to find broad acceptance despite available clinical data and even POC technology due to the limitations of a single biomarker in such a context. Newer candidates are on the horizon with added consideration on logistics and resource requirements. They may play a key role for acceptance into routine clinical practice in the near future.

A key point mentioned in the ADQI consensus statement is the combination of patient factors and diagnostic findings which need to be reviewed in acute illness context. Biomarkers should support a patient-specific approach rather than a general diagnostic or prognostic threshold. Within Fresenius Medical Care, we are engaged in biomarker research through our clinical evidence generation programs as well as work done at the Renal Research Institute, which not only looks at novel biomarkers as such but also at mathematical assessments and modelling of biomarker data to improve the utility of such markers. Therefore, we are certainly at the forefront of such research but it will require more scientific and clinical work before such biomarkers will become standard of care.

References:
(1) Acute Kidney Injury Work Group, *Kidney Int Suppl* 2012;2:1–138; (2) Bellomo R et al, *Crit Care* 2004;8(4):R204-12; (3) Mehta R et al, *Crit Care* 2007;11(2):R31; (4) Levey S et al, *Eur Heart J* 2020;41(48):4592-4598; (5) van Duijl T et al, *Clin Biochem Rev* 2019;40(2):79-97; (6) Gomez H et al, *Shock* 2014; 41(1):3-11; (7) Dobrek L, *Life (Basel)* 2021;11(3):208; (8) Ostermann M et al, *JAMA Network Open* 2020;3(10):e2019209; (9) Molinari L et al, *JAMA Network Open* 2022;5(5):e2212709; (10) Bhosale S, Kulkarni A, *Indian J Crit Care Med* 2020;24(Suppl 3):S90-S93; (11) Meersch M et al, *Intensive Care Med* 2017;43(11):1551-1561; (12) Gardner D et al, *Kidney Int Rep* 2022:7;1524–1538; (13) Sparding N et al, *KIDNEY360* 2022:3; 809–817; (14) Stanski N et al, *Pediatr Res* 2022, doi: 10.1038/s41390-022-02233-2.