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Urinary Biomarkers IGFBP-7 and TIMP-2 for AKI Risk Stratification: Are we there yet?

Sonu Bhatnagar*

Commentary

Improving Global Outcomes (KDIGO) [1] recently published practice guidelines for identification and treatment of patients with acute kidney injury (AKI). One important recommendation from the KDIGO guidelines was the development of biomarkers that identify AKI prior to elevations of serum creatinine, which can take days to manifest.

AKI is one of the most common organ dysfunctions in critically ill patients [2] which adversely impacts short- and long-term clinical outcomes. It is frequently observed in patients after cardiac surgery (CS) involving cardiopulmonary bypass (CPB) [3]. Early diagnosis of AKI, preferably within 24 hours after ICU admission, is likely pivotal to the development of effective therapies. Traditional biomarkers like creatinine are late indicators of AKI, delaying diagnosis by days.

Several biomarkers for predicting AKI were identified during the last decade, but none reached an acceptable level of suitability or precision [4]. Many AKI biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin (IL)-18 and kidney injury molecule-1 (KIM-1) have been unreliable in the real world setting of general ICU patients [5]. A recent multicenter international investigation, the Sapphire study, reported the discovery and validation of two G1 cell-cycle arrest biomarkers (CCABs), tissue inhibitor of metalloproteinases (TIMP-2) and insulin-like growth factor binding protein (IGFBP-7) [6]. When combined, these CCABs detected AKI with a high level of accuracy and were found excellent in identifying patients at imminent risk of severe AKI [6].

IGFBP-7 is a secreted glycoprotein that binds to insulin growth factors [7]. According to the Human Protein Atlas, IGFBP-7 is expressed in glomeruli and tubules of healthy humans and plays an important role in G1 cell-cycle arrest. Renal tubular cells can enter a short period of G1 cell-cycle arrest following injury from experimental sepsis [8] or ischemia [9]. This process may prevent cells from dividing when DNA is damaged and may represent an early response to renal injury. TIMP-2 is another protein involved in cell-cycle arrest, suggesting the importance of this process in AKI. Kashani et al. [6] examined around 340 biomarkers in critically ill patients at risk for AKI. IGFBP-7 and TIMP-2 outperformed other markers of AKI including urine/plasma NGAL, urine KIM-1, urine interleukin-18, plasma cystatin C, and serum creatinine and had an AUC of 0.8 for predicting AKI onset 12–36 h after sample collection. It is notable that IGFBP7 and TIMP-2 are both involved with the phenomenon of G1 cell cycle arrest during the very early phases of cell injury.

AKI engages a series of extremely complex cellular and molecular pathways involving endothelial, epithelial, inflammatory, and interstitial cells. These mechanisms include cell cycle, immunity, inflammation, and apoptosis pathways. Prior efforts at identifying biomarkers for AKI have been hampered by this heterogeneous nature of the condition. In any given patient, the cause for AKI onset is typically thought to be multifactorial.

Interestingly, the reported biomarkers performed very well in patients with sepsis (AUC 0.82) and post-surgery (AUC0.85). The study showed IGFBP7 is superior to TIMP-2 in surgical patients while TIMP-2 is best in sepsis-induced AKI. These differences may underlie subtle but important mechanistic differences between various etiologies of AKI, and that the two biomarkers are involved in slightly different pathways.

To guide the clinical use of these two markers for risk assessment, Bihorac et al. [10] selected a high-sensitivity cutoff using the results of their earlier studies [6]. They studied 420 critically ill adult patients within 24 hours of admission to an intensive care unit (ICU). Critically ill patients with urinary [TIMP-2]*[IGFBP7] test values greater than 0.3 had seven times the risk for AKI (95% CI, 4–22) compared with those with a test value at or below the 0.3 cutoff .The secondary analysis of this urinary test at a cutoff of 2.0 demonstrated specificity of 95% and sensitivity of 37%. When patients were stratified by both cutoffs, the relative risk for AKI increased proportionally.

The fact that in the presence of clinical risk factors for AKI like hypotension or hypoxemia, it is difficult to discriminate those who will imminently develop AKI from those who will not. Addition of the urinary [TIMP-2]*[IGFBP7] test increased the AUC of the clinical model from 0.70 to 0.86 while stratifying patients in more distinct risk categories, with a sevenfold increase in risk for patients in the high-risk group compared with those in the lowest.

AKI remains one of the most common complications among hospitalized patients [2,11]. Few risk stratification models based on clinical factors exist and they are generally inadequate in accurately identifying individual patients at risk. Thus, the ability to identify patients at risk for imminent AKI has been elusive and represents an important unmet need [11].

But the efforts to reproduce the same results as of previous studies have been controversial. There are notable differences when comparing the original discovery and validation investigations with Bell et al. study [12], even though both were done in general ICU cohorts. [TIMP-2]*[IGFBP7], NGAL, or cystatin-C admission levels did not differ between patients without AKI and patients developing AKI in Bell et al study. They observed that [TIMP-2]*[IGFBP7], NGAL, and cystatin-C were poor AKI predictors (ROC areas 0.34–0.51). Their data suggest that when measured by a commercial point-of-care device, the novel CCABs, NGAL, and urinary cystatin C failed to predict evolving AKI in a general cohort of ICU patients. Their findings also suggest that the new markers performance may decrease markedly in general ICU patients, with heterogeneous diagnoses, differing comorbidities, and

***Corresponding author:** Sonu Bhatnagar, Scientific Affiairs, Sysmex Asia-Pacific Pte Ltd, 9 Tampines Grande, #06-18, Singapore-520735, Tel: +65 91550275; E-mail: Bhatnagar.sonu@sysmex-ap.com

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multiple sources of inflammation pointing towards the multifactorial etiology of AKI.

In yet another study by Wetz et al. [13], the researchers failed to identify AKI risk 4 hours after CPB which was reported by Meersch et al. [14]. Compared to surgical procedures with valve or combined surgery, CABG-only surgery requires shorter CBP and ACC time, assuming lesser injury to the kidneys. So, it is possible that the AKI of lesser severity reached in Wetz et al.' patient population was due to different surgical conditions and not of a time frame within which the biomarker concentration rises to a significant level at early measurement time points. The risk of injury to the kidneys could have been considerably higher in the trial of Meersch et al. [14] than in Wetz et al. study, because they also included patients undergoing valvular and combined surgeries with assumed higher risks of kidney injury due to longer CBP and ACC times than observed in Wetz et al. patient population (140 and 98 minutes vs. 127 and 78 minutes, respectively). This may have led to the divergent results and may be a reason why the trials of Kashani et al. [6] and Meersch et al. [14], who included only patients at higher risk for AKI, showed more precise results of the biomarker test. Because the test was not perfectly applicable to Wetz et al. patient cohort of mainly low-grade kidney injury (KDIGO 1) and Kashani et al. proved good results on KDIGO 2 and 3, the question arises whether the biomarker test might be better applicable for predicting high-grade kidney injury [6].

Wetz et al. also could not be confirm previously reported cutoff points of 0.3 and 2 [6] in their study cohort. Applying the low cutoff point resulted in a sensitivity of 53% and a specificity of 54%. The cutoff point of 2 led to a sensitivity of 33% and a specificity of 100%. In contrast, in their study, they found a cutoff point of 1.1 with an AUC of 0.71 (46.67% sensitivity, 96.15% specificity). The reason for this finding may lie again in different patient cohort composition and different surgical settings, as well as their smaller number of patients, which surely led to weaker results.

In conclusion, clinical markers of kidney function often fail to detect AKI at a time when interventions may provide benefit. Urinary [TIMP-2]*[IGFBP7] test has been observed to add value to clinical model of risk stratification. However, the value of successfully predicting AKI by these novel biomarkers at this time point needs further assessment. Before broader routine clinical implementation, a thorough analysis of the diagnostic strength of these new biomarkers to accurately predict AKI should be established in further trials.

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