

EDITORIAL COMMENT

Can Novel Biomarkers Complement Best Possible Clinical Assessment for Early Acute Kidney Injury Diagnosis?*

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The early diagnosis of acute kidney injury (AKI) appears now to be within reach, and some already suggest integrating novel urinary biomarkers in current AKI classification systems (1,2). Conventional AKI definition relies on markers of renal function (Risk, Injury, Failure, Loss, and End-Stage Kidney Disease [RIFLE], Acute Kidney Injury Network [AKIN]), and diagnosis is therefore often delayed, perhaps contributing to the unfavorable clinical course of affected patients. Specifically, serum creatinine requires several hours to days to accumulate, it increases in serum only after 50% or more of renal function is lost, and its concentration is affected by multiple confounding factors. Urine output, another potential diagnostic biomarker, has limited sensitivity (3).

See page 2301

Although evidence from numerous studies (4,5) for the usefulness of novel AKI biomarkers already exists, only a minority of institutions permanently use biomarkers to make early AKI diagnosis part of daily clinical routine. Such incomplete implementation may be explained by some heterogeneity in the reported predictive ability of biomarkers, which is in part related to the use of different AKI definitions (6) or conditions of sample storage (7). As another source of heterogeneity, Thurman and Parikh (8) proposed that the timing of measurement is of importance for the predictive ability of AKI biomarkers. This aspect of

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biomarker utility has now been confirmed in the study by Krawczeski et al. (9) in this issue of the *Journal*.

In this study (9), 4 of the most promising noninvasive urinary biomarkers (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule [KIM]-1, liver-type fatty acid-binding protein [L-FABP], and interleukin [IL]-18) were investigated in a cohort enrolling 220 children without pre-existing chronic kidney disease and other major comorbidities. All patients underwent cardiac surgery with the use of cardiopulmonary bypass, and all biomarkers were measured 4 times within 24 h.

The authors found a temporal relationship of the predictive value of these urinary biomarkers and their combination. Specifically, NGAL was the only biomarker with predictive value as early as 2 h post-operatively (9), whereas the other biomarkers had no value at this early time point. The predictive value of NGAL was very good (area under the curve receiver-operator characteristic [AUC-ROC] >0.9) and independent of the timing of its measurement, with only minimal improvement over time within the first 24 h. The AUC-ROC values of urinary KIM-1, L-FABP, and IL-18 slowly progressed and reached good value at 12 to 24 h post-operatively, at a time where, in 98% of patients, clinical AKI diagnosis was already made. At 6 h and even more so at 24 h, a combination of renal biomarkers showed a slightly increased predictive value for AKI as compared with a single biomarker. Importantly, addition of biomarkers resulted in a considerable improvement in early AKI diagnosis over a clinical model including age and cardiopulmonary bypass time (net reclassification improvement [NRI] at 2 h: NGAL +87%, IL-18 +14%, L-FABP +17%, and KIM-1 -3%).

The results of this study are novel with regard to the effect of timing and combination of 4 urinary biomarkers; they are confirmatory in nature, showing the potential importance of biomarkers in addition to current AKI diagnosis (10). Just recently, Parikh et al. (11) also showed, in a multicenter study, that, when added to clinical risk prediction, urinary NGAL and IL-18 improved risk classification in pediatric patients after cardiac surgery. However, compared with other studies, Krawczeski et al. (9) reported very high NRI values using no risk categories, as these are currently not established in the field of AKI. The reported different NRI values for the same marker added to different models with different numbers of risk categories should be taken into consideration when comparing and interpreting findings across various studies and settings.

Is it worth it to measure a *panel* of biomarkers, and if so, which patients might benefit from such measurements? At this stage, there seems to be no convincing evidence that, in addition to NGAL, the performance of biomarker panels is more effective or efficient in early AKI diagnosis.

This study (9) may be criticized because other urinary biomarkers, such as cystatin C, another promising tubular biomarker, were not included, and the generalizability of the

present study is limited due to the fact that only approximately 60% of patients with less severe cardiac and renal disease were retained for the analysis. In addition, although children are an ideal type of patient in whom to study AKI biomarkers without the influence of comorbidities, findings in pediatric studies have limited transferability to adult patients.

In most biomarker studies—as was done in the present study (9)—a creatinine-based AKI definition was used. However, in clinical practice, the evaluation of whether a patient developed AKI or not is complex. Such evaluation includes the assessment of changes in urine output and serum creatinine according to consensus criteria, but also includes assessment of the slope of creatinine increase and adjustment for its modification by confounding variables (e.g., by hemodilution induced by fluid therapy). Furthermore, other aspects of clinical assessment include urine output in relation to fluid input adjusted for dose of diuretics, the assessment of hemodynamic variables, and the sum of other risk factors for AKI (signs of inflammation, shock, overhydration/dehydration or rhabdomyolysis; metabolic acidosis; use, dose, and timing of nephrotoxins; comorbidities). All these aspects are integrated for the best possible clinical assessment in making an early AKI diagnosis. In the absence of a definitive test for early AKI diagnosis at the bedside, the more experienced the physician is, the greater the likelihood for a reasonable diagnostic assessment. Such experienced clinicians may allocate limited value to the use of biomarkers, as was initially the case for troponin or brain natriuretic peptide. Yet, such cardiac biomarkers have been shown to be superior to clinical assessment in the diagnosis of myocardial infarction or decompensated heart failure (12). It is possible, maybe likely, that renal biomarkers will similarly outperform clinicians in the diagnosis of imminent AKI.

Many types of applications for AKI biomarkers have been recently tested and found superior to standard clinical assessment, including their use to predict the need for renal replacement therapy (13) and recovery from it (14), the differential diagnosis of serum creatinine increase in patients admitted to an emergency department (5), the selection criteria for a subsequent intervention (15), or the ability to deliver therapeutic monitoring (16). The predictive value of NGAL for early AKI diagnosis and prognosis has been summarized in a meta-analysis (4). Finally, measurement of NGAL in patients at risk of AKI identifies a population with likely organ injury that cannot be identified by other tests (1). Such findings suggest that the addition of structural renal damage markers to AKI consensus definition needs to be seriously considered.

A proof-of-concept trial randomizing patients to AKI biomarker measurement with subsequent classical nephrological measures is still lacking. However, achieving such demonstration of therapeutic utility is a complex task, and if achieved, it would go a step further than any other renal biomarker (including creatinine, urea, and urine output) has needed to go in the past.

Given the previous considerations, biomarkers with a clear cut-off may: 1) complement a standardized but still simple diagnostic approach to AKI; 2) help young clinicians improve their ability to make an early AKI diagnosis; and 3) perhaps even add to the diagnostic accuracy of experienced physicians. AKI biomarkers have not yet been compared with such a complex endpoint of AKI diagnosis (“best possible clinical guess”), as described earlier. Beyond complementing physician judgment, the potential advantage of biomarkers is that they are developed to individually indicate the presence of actual renal damage.

In conclusion, the study by Krawczeski et al. (9) in this issue of the *Journal* demonstrates promising biomarkers in the early diagnosis of AKI in children with congenital heart disease.

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