INVITED COMMENTARY

Biomarkers in Acute Kidney Injury: The Hope, the Hype and the Promise

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The diagnosis of acute kidney injury (AKI), a heterogenous and complex clinical entity associated with mortality up to 60% in critically ill patients, continues to pose many challenges. Although the Kidney Diseases Improving Global Outcomes (KDIGO) definition of AKI is now standardized [1], it continues to have fallacies since serum creatinine and urine output have limitations in defining and staging AKI. Serum creatinine and urine output are functional markers of AKI, and not early markers of kidney injury [2]. Moreover, serum creatinine is influenced by factors unrelated to glomerular filtration rate, e.g., low muscle mass, tubular secretion of creatinine, nephron reserve, intravascular volume status, fluid shifts and hemodynamic changes [3]. Serum creatinine cannot unilaterally help in taking major treatment decisions such as kidney replacement therapy in AKI, without consideration of the patient's clinical status. Moreover, due to analytical and biological variations, serum creatinine can still sometimes fulfil the 0.3 mg/dL rise from baseline criterion for AKI, even if actual injury to the nephrons has not occurred. Additionally, serum creatinine increases quite late after kidney injury and this rise is often not proportionate to the degree of kidney injury. These aspects have motivated many researchers to seek other biomarkers that might be indicative of early nephron injury [4].

What is the position of these AKI biomarkers currently?

Many kidney injury biomarkers have crossed the mileposts for use in clinical care. These include established cutoff values from various studies, and inclusion of external validation cohorts. There are many clinical scenarios where AKI biomarkers are available or approved for usage in clinical care. For example, urine Neutrophil gelatinase-associated lipocalin (NGAL) in cirrhosis with AKI, inflammatory biomarkers (urinary CXCL9, TNF-α, and IL-9) in patients with acute interstitial nephritis, and the kidney safety panel (urine clusterin, KIM-1, NGAL, NAG, cystatin C, and osteopontin) are ready for clinical care and might potentially guide management [4]. In other scenarios, biomarkers are at different levels of development and may take time for clinical care implementation [5]. The impact of these biomarkers on patient outcomes however, needs evaluation in future studies.

A recent systematic review and meta-analysis concluded that urine NGAL, liver-type fatty acid-binding protein (L-FABP), cystatin C, and tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein 7 (TIMP-2*IGFBP7) showed satisfactory performance in predicting AKI early [6]. In order to augment the performance of biomarkers, they may be integrated with renal angina index. A combination of biomarkers may also lead to earlier identification of AKI.

Recent literature as well as the US Food and Drugs Administration (FDA) support the usage of NGAL and TIMP-2*IGFBP7 as biomarkers for diagnosis of AKI [7]. TIMP-2 and IGFBP-7 (known as *Nephro-check*) are two new cell cycle arrest biomarkers and have been termed as the 'renal troponin'. In December 2023, the United States Food and Drug Administration (US FDA) also affirmed the usage of urine NGAL for evaluation of severe AKI risk within 48 to 72 hours in the pediatric population. NGAL is a 25-kDa glycoprotein attached to neutrophil gelatinase, and found in proximal tubular epithelial cells, stomach, lungs and colon. At early stages of AKI, nephrotoxic or ischemic kidney injury may lead to expression of NGAL. NGAL levels increase within 3 hours after kidney injury and attain peak levels at 6 hours. These levels might remain high even upto 5 days. A recent systematic review and meta-analysis found no significant difference in predictive accuracy between urine and blood NGAL levels [8]. In another meta-analysis, urine NGAL exhibited excellent diagnostic qualities after pediatric cardiac surgery. However, the authors noted that more consolidatory evidence will be needed before they can be used precisely in patient management [9].

In this issue of *Indian Pediatrics*, El-Halaby *et al* [10] evaluated the efficacy of plasma NGAL for early prediction of AKI in 174 children aged 6-60 months undergoing cardiopulmonary bypass (CPB) for congenital heart disease,

in a prospective observational study. Plasma NGAL was measured preoperatively and at 2, 12, 24, 36, and 48 hours post-CPB. The incidence of AKI was 34.5%. Plasma NGAL levels post-CPB were significantly higher in AKI and positive correlations between plasma NGAL level and severity of AKI were observed. A 5-times elevation in plasma NGAL at 2 hours post-CPB from its baseline pre-operative level (termed NGAL 2-0 index) was an early predictor of AKI. The authors calculated an NGAL index instead of a particular cut-off value for plasma NGAL, which adds new information regarding how the trends in this biomarker could contribute to early diagnosis of AKI. Although the authors state that this may permit earlier intervention that improves the outcome of AKI, this aspect appears to be speculative as the impact of any such potential interventions on clinical outcomes were not studied. Nevertheless, the study is appreciable for recruiting a large number of children undergoing CPB in a prospective manner.

Why have biomarkers in AKI been able to penetrate clinical settings in a limited manner only?

In spite of large-scale and substantial research efforts worldwide, as well as availability of the aforementioned systematic reviews and meta-analysis on biomarkers in AKI [6,8], few clinicians order AKI biomarkers in day-to-day clinical practice. Perhaps, estimation of prognostic value, that has been the cornerstone of the overwhelming literature on biomarkers in AKI, is a substantial element, but not enough to be termed as sufficient. An AKI biomarker that is deemed clinically useful should provide new and reliable information that helps in changing the clinician's decision-making abilities (e.g., initiation or discontinuation of dialysis, kidney biopsy, corticosteroid usage, etc.) and translate into optimal clinical care without harming the patient. Therefore, future studies should move beyond the point of establishing prognostic significance of biomarkers alone. In fields outside pediatric nephrology, biomarkers such as procalcitonin in sepsis, and troponin T in myocardial dysfunction have been used to guide clinical decisions. In contrast, biomarkers for diagnosis and management of AKI have a long journey ahead.

The importance of studies conducted for diagnostic accuracy of newer biomarkers cannot be undermined, but additional measures are required, such as randomized-controlled biomarker-strategy trials to make them useful to clinical situations. There is hope that the care of patients with AKI can significantly improve if such trials are conducted [11]. Though some authors have been skeptical of biomarkers in AKI as being 'an innovation desperately in search for an indication'[12], this approach appears to be too pessimistic.

The advent of cell cycle arrest markers that estimate cellular stress prior to the kidney injury phase is a promising development [7]. However, we have to be cognizant of the fact that the vast paraphernalia of newer biomarkers in AKI have not been able to dethrone the 'humble' creatinine; and this metabolite continues to retain its prominence for the diagnosis of AKI, and its monitoring. This is because the practical utility of the newer biomarkers of AKI in the form of their impact on patient outcomes has not been established. This aspect requires rigorous evaluation in further studies. It is possi-ble that we might get a definitive and 'ideal' biomarker of AKI in the future, but currently we have not reached that stage.

Funding: None; *Competing interest*: None stated.

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