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EDITORIAL

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Biomarkers for AKI improve clinical practice: no

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Despite recent developments in definition and staging, the diagnosis of (AKI) acute kidney injury is still based on oliguria and/or an increase in serum creatinine [1]. Consequently, research in the last decade has focussed on the discovery and validation of more specific and sensitive markers of tubular damage/functional impairment. The most advanced biomarkers promise to identify patients at risk of AKI, diagnose AKI earlier than conventional tests and prognosticate risk of progression, including need for (RRT) renal replacement therapy [2–16]. The hope is that, with such an approach and more timely and relevant interventions, the outcome of patients with AKI can be improved. Commercial biomarker kits are now available in most countries. However, like any other new diagnostic test, these novel AKI biomarkers need to add value above and beyond currently available tools, before being incorporated into routine clinical practice. It is therefore essential to have a close look at the expectations of AKI biomarkers and their actual performance and potential role in practice.

1. Can novel AKI biomarkers help to identify high-risk patients? In principle, it is appealing to identify high-risk patients, especially if this provides an opportunity to intervene and prevent the event of interest. In the case of AKI, the currently recommended preventative strategies include optimisation of haemodynamics and volume status and avoidance of further harm, i.e. avoidance of nephrotoxic drugs, contrast media, or starches [1]. One could easily argue that this should be done in any critically ill patient, regardless of whether or not they are at high risk of AKI, and that therefore the information from a new biomarker test is redundant.

Ideally, a test to identify high-risk patients should be as reliable as possible to avoid false positive and false negative results. Experience from other clinical areas has taught that non-selected use of biomarkers like prostate-specific antigen or d-dimer in an unselected population produces a high number of false positive results and can potentially lead to harmful and unnecessary interventions. In the case of AKI, the area under the receiver operating characteristics curves of some biomarkers look impressive but the clinical application of the results to individual patients is hampered by wide overlap between groups. Similarly, biomarker studies vary in their cut-offs between positive and negative results (Table 1). As a result, potential harm may occur if important interventions (i.e. computed tomography with contrast or necessary administration of aminoglycosides) are being delayed or withheld based on false positive biomarker results.

Some biomarkers, for instance plasma neutrophil gelatinase-associated lipocalin (NGAL), reflect a general degree of severity of disease, rather than being specific for kidney injury [4, 17, 18]. In this case, the role of kidney-specific preventative measures is questionable.

Table 1 Characteristics of the most studied biomarkers for AKI

AKI biomarker	Biological origin	Renal specificity	Clinical utility[a]			Common confounding factors	Additional comments
			Prediction of AKI	Prediction of AKI progression/RRT	Prediction of mortality		
NGAL	Leukocytes and epithelial cells in kidneys, spleen and liver	No	(i) Children post-cardiac surgery [2]: AUROC 0.998 (urine NGAL cut-off >50 ng/ml; AKI defined as 50 % rise in creatinine from baseline) (ii) Adults post-cardiac surgery [3]: AUROC 0.60 (urine NGAL cut-off >450 ng/ml; AKI defined by AKIN criteria) (iii) Adults admitted to ICU with sepsis [4]: AUROC 0.67 (plasma NGAL cut-off >73.5 ng/ml; AKI defined by AKIN and RIFLE criteria) (iv) Non-selected critically ill patients [2]: AUROC 0.73 (plasma and urine NGAL cut-off 155 ng/ml)	(i) Children post-cardiac surgery [2]: AUROC 0.80–0.90 depending on timing of measurement (urine NGAL cut-off >150 ng/ml) (ii) Across different AKI settings [2]: AUROC 0.78 (NGAL cut-off >278 ng/ml)	(i) Children post-cardiac surgery [2]: AUROC 0.67–0.91 depending on timing of measurement (urine NGAL cut-off >150 ng/ml) (ii) Across different AKI settings [2]: AUROC 0.71 (NGAL cut-off >212 ng/ml)	Sepsis malignancy CKD	1. NGAL exists as a 25-kDa monomer, 45-kDa homodimer and as a 135-kDa heterodimeric form 2. Detectable in plasma and urine
Cystatin C	Produced by all nucleated human cells	No	(i) Adults post-cardiac surgery [5]: AUROC 0.74 (AKI as per AKIN criteria) (ii) Elderly patients undergoing cardiac surgery [6]: AUROC 0.77 (AKI as per RIFLE criteria) (iii) Adults presenting to the emergency department [7]: AUROC 0.87 for serum cystatin C; AUROC 0.57–0.61 for urine cystatin C (AKI as per AKIN criteria)	(i) Adults with AKI [8]: AUROC 0.65	(i) General ICU patients [9]: AUROC 0.64	Systemic inflammation malignancy smoking	Detectable in plasma and urine
KIM-1	Proximal tubular cells	Yes	(i) ICU patients with sepsis [10]: AUROC 0.3–0.9 depending on timing of measurements (ii) Adults and children post-cardiac surgery [11]: AUROC 0.78 if measured between 6–12 h postoperatively (AKI defined as doubling of serum creatinine or need for RRT)	(i) Critically ill adults with early AKI [12]: AUROC for progression, RRT or death 0.65 (ii) Patients post-cardiac surgery with AKI stage I [13]: AUROC 0.73	(i) Critically ill adults with early AKI [12]: AUROC for progression, RRT or death 0.65 (ii) Patients post-cardiac surgery with AKI stage I [13]: AUROC 0.81	CKD proteinuria	Detectable in urine
L-FABP	Liver, lung, intestine, pancreas, nervous system, proximal tubular cells	No	(i) Adults and children post-cardiac surgery [11]: AUROC 0.78 if measured from day 2 postoperatively (AKI defined as doubling of serum creatinine or need for RRT)	(i) Critically ill adults with early AKI [12]: AUROC 0.79 for progression, RRT or death (ii) Patients post-cardiac surgery with AKI stage I [13]: AUROC 0.85 for progression to AKI stage 3 or death			Detectable in plasma and urine

Table 1 continued

AKI biomarker	Biological origin	Renal specificity	Clinical utility[a]			Common confounding factors	Additional comments
			Prediction of AKI	Prediction of AKI progression/RRT	Prediction of mortality		
[IGFBP7] X [TIMP-2]	Tubular cells	Yes	(i) Critically ill patients [14, 15]: AUROC 0.80 for development of AKI stage II or III within 12 h (ii) Critically ill patients [16]: AUROC 0.86 when combined with clinical factors [cut-off value >0.3 $(ng/ml)^2/1{,}000$]	(i) Critically ill patients [14]: doubling of risk of MAKE30 for cut-off value >2 $(ng/ml)^2/1{,}000$ MAKE30 = major adverse kidney event (need for dialysis, mortality or doubling of serum creatinine) at 30 days			Detectable in urine

AKI acute kidney injury, *AKIN* acute kidney injury network, *AUROC* area under the receiver operating characteristic curve, *CKD* chronic kidney disease, *ICU* intensive care unit, *IGFBP7* insulin-like growth factor binding protein 7, *KIM-1* kidney injury molecule 1, *L-FABP* L-type fatty acid-binding protein, *MAKE30* major adverse kidney event at 30 days, *NGAL* neutrophil gelatinase-associated lipocalin, *RIFLE* risk–injury–failure–loss–endstage kidney disease, *RRT* renal replacement therapy, *TIMP-2* tissue metalloproteinase-2

[a] Selected examples of studies to underpin the arguments in main manuscript

Finally, the performance of most biomarkers for AKI is better in selected patient groups at high risk of AKI. For instance, the recently FDA approved Nephrocheck®, which measures two cell cycle arrest markers, insulin-like growth factor binding protein 7 and tissue metalloproteinase-2, was evaluated and validated in critically ill patients in the intensive care unit (ICU) [14, 16]. Whether it performs equally well in unselected cohorts like patients in non-ICU wards or the emergency department remains to be seen.

2. Can novel AKI biomarkers diagnose AKI earlier than traditional tests? Several biomarkers have been shown to indicate the onset of AKI before serum creatinine rises. The results are most impressive in paediatric cohorts without comorbidities suffering from an illness with a defined onset of AKI, for instance in children after cardiac surgery [2] (Table 1). In more heterogeneous populations, where the onset of renal injury is not known (i.e. patients with septic shock), the performance of some biomarkers to detect AKI earlier was equivalent to clinical evaluation and standard laboratory measurements but not significantly better [3, 4].

It is generally assumed that an earlier diagnosis of AKI automatically translates into earlier treatment and better patient outcome. Unfortunately, there is currently no evidence that this is indeed the case. Also, there is no specific therapy for AKI. To date, the management of AKI is supportive with emphasis on optimisation of haemodynamic and fluid status and avoidance of further nephrotoxic insults [1], i.e. strategies which should form part of good critical care in all patients at any time.

3. Can novel AKI biomarkers identify patients who need RRT? Predicting whether patients will progress to needing RRT confronts us with a similar conflict as predicting who will develop AKI. To date, there are no interventions beyond treatment of the underlying illness, attention to detail and good medical care which prevent progression of AKI or induce recovery. Although it may appear attractive to know which patient will need RRT, this knowledge is unlikely to change clinical practice, especially since there is no evidence that starting RRT earlier before it is needed by current criteria is beneficial [19]. However, knowing whether a patient on RRT has recovered sufficient native renal function so that RRT can be stopped would be useful but, to date, none of the available biomarkers are capable of doing so.

4. Do novel AKI biomarkers improve patient outcome? No biomarker has yet shown the efficacy of any intervention based on increased biomarkers. The only intervention study using biomarkers to guide treatment was negative [20]. Therefore, the claim that biomarker use benefits patients and improves outcome remains unproven.

5. When should AKI biomarkers be measured? One of the difficulties in utilizing AKI biomarkers has been to identify which patients would benefit most. Some studies advertise the use of biomarkers in situations where the outcome already seems predictable based on standard parameters, such as clinical appraisal and oliguria. Clearly, in this situation, there is little added benefit. Similarly, indiscriminate application of biomarkers in patients at low risk of AKI would also render the biomarker useless, as well as unnecessarily increase healthcare costs.

There are additional methodological problems in biomarker research leaving clinicians with uncertainty. First, in the majority of studies, the performance of novel biomarkers was judged by comparison with serum creatinine and oliguria, two markers which are affected by confounding factors and often proclaimed to be not sufficiently kidney-specific. Second, studies vary in the chosen cut-offs to establish thresholds for negative and positive predictive events related to AKI (Table 1). Third, there is uncertainty regarding the exact laboratory method, the assay platform and sampling conditions and whether biomarker levels should be normalised for urinary creatinine [17, 18]. Fourth, like creatinine, several novel biomarkers of AKI are themselves not renal-specific and confounded by common comorbid conditions, for instance sepsis and chronic kidney disease (Table 1). Finally, most biomarkers demonstrate a dynamic pattern reflective of the molecular and cellular events that occur throughout the clinical phases of AKI. It is therefore likely that a panel of different biomarkers and multiple measurements will be necessary rather than a single test. Whether the associated costs and turn-around time are realistic in clinical practice is questionable.

We acknowledge that some studies have shown very impressive results and agree that biomarkers have the potential to transform the way we diagnose and treat patients with AKI. However, at this stage, there are still too many unresolved concerns and uncertainties which hamper their clinical applicability.

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