Biomarkers of acute kidney injury: time to learn from implementations

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Acute kidney injury (AKI) is a major clinical problem in the community and in hospital, with hospital-acquired AKI reported in about 20% of adult and 30% of paediatric admissions.[1,2] Laboratory creatinine data from New South Wales support these figures: 16.4% of patients and 12.4% of hospitalisations developed AKI over a 5-year period.[3] This study also highlighted the under-reporting of AKI in Australia based on coding of the International Classification of Diseases, tenth revision, Australian modification (ICD-10-AM) (1.6% incidence) versus laboratory creatinine-based diagnosis (12.4%). In addition, AKI leads to the development of chronic kidney disease (CKD) in many survivors.[4-6] However, the true incidence of kidney damage following AKI may be even greater, since overt or subclinical AKI may lead to subclinical CKD, which in turn may precede overt CKD.[7] Without measuring renal reserve or performing renal biopsy, subclinical CKD remains undetected, as creatinine remains normal by definition. Along with overt CKD, subclinical CKD remains a risk factor for AKI following repeated kidney exposure to injury.[7] Unfortunately, an inevitable delay in diagnosis is inherent in the functional definition of AKI as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[8] This delay results from creatinine kinetics,[9] with the result that creatinine-based diagnosis has never and will never lead to successful intervention trials in AKI. However, this definition is likely to change because of the recognition that kidney damage biomarkers offer near real-time detection of kidney cellular injury.

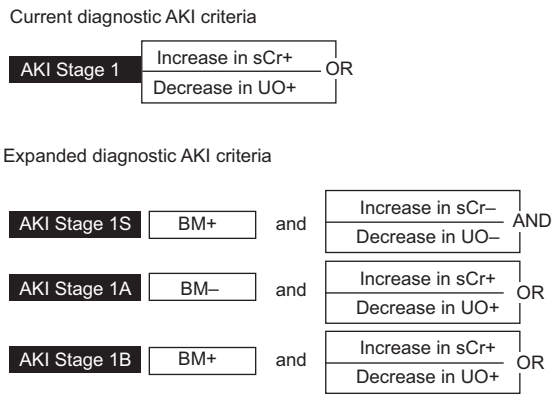
Several biomarkers have been shown to detect AKI from hours to days earlier than serum creatinine. These include previously recognised proximal tubular proteins, such as enzymes released from damaged epithelial cells (eg, γ-glutamyl transpeptidase [GGT])[10] to more novel proteins upregulated by injury in kidney epithelial cells (eg, kidney injury molecule 1 [KIM-1] and neutrophil gelatinase-associated lipocalin [NGAL]) shed into urine, to circulating or filtered markers of inflammation, apoptosis and fibrosis (eg, various microRNA molecules) and filtered markers of cell stress (eg, the cell cycle inhibitors, tissue inhibitor of metalloproteinase 2 [TIMP-2] and insulin-like growth factor-binding protein 7 [IGFBP7]). Such stress or damage biomarkers usually increase before any change in creatinine is measurable[11] and in critical illness,[12] and provide a window of opportunity for early intervention.[13]

Recognition that biomarker (BM)-positive/serum creatinine (Cr)-negative subjects have the same risk of subsequent dialysis and death as subjects in whom creatinine alone is increased has led to the recognition that BM+/Cr– subjects have (by a creatinine-based definition) a subclinical category of AKI.[14,15] Subsequent studies have verified these conclusions in children.[16,17] Adults with subclinical AKI after cardiac surgery also have increased mortality up to 7 years later.[18]

Therefore, the next step in the evolution of the definition of AKI is the incorporation of damage biomarkers into the day-to-day definition of AKI used in clinical practice. The simplest step is a matrix of four categories: no AKI (BM–/Cr–), subclinical AKI (BM+/Cr–), perfusion-dependent AKI (BM–/Cr+), and severe AKI (BM+/Cr+).[19,20] As expected, the severe category is associated with more severe outcomes,[15] and combining functional and damage biomarkers improved diagnostic precision.[16] However, wider implementation outside a research setting has awaited validation of appropriate biomarker thresholds for each novel damage biomarker in a range of relevant clinical AKI contexts.[21]

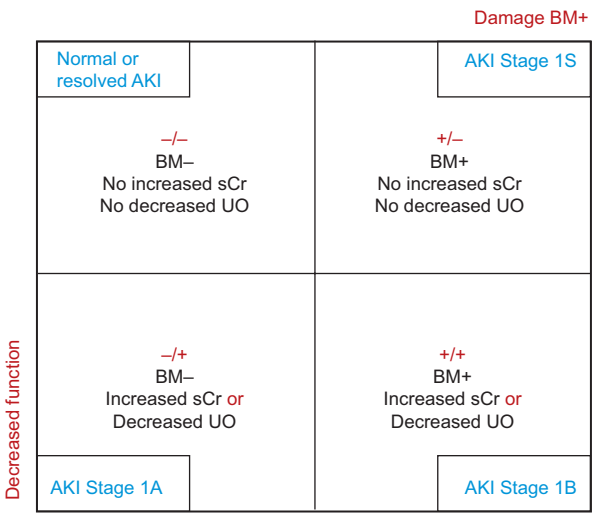
Biomarker thresholds have now been validated in global studies for NGAL[22] and several have been approved and entered regular clinical practice: NGAL in Europe,[23] [TIMP-2]·[IGFBP7] (marketed as NephroCheck, Biomérieux) in the United States[24] and Europe,[25] and liver-type fatty acid-binding protein (L-FABP) in Japan.[26] NephroCheck received approval from the US Food and Drug Administration for early diagnosis and prediction of progression to more severe AKI.[24] These observations suggest that these biomarkers are ready for inclusion in clinical practice. For example, triaging with urinary [TIMP-2]·[IGFBP7] immediately after cardiopulmonary bypass has led to simple and successful intervention by targeted application of KDIGO guidelines, with 33% and 35% reductions in moderate (Stage 2) and severe (Stage 3) AKI respectively.[27] Similar benefits

Figure 1. Current and expanded criteria for acute kidney injury (AKI) diagnosis



+ = positive; – = negative; BM = biomarker; sCr = serum creatinine; UO = urine output criteria. Patients with a BM of injury positivity without increase (or decline) in sCr level and not reaching UO criteria should be classified as Stage 1S. Reassessment is recommended according to clinical context and temporal trends. Patients reaching sCr and UO criteria with no increase on BM are defined as Stage 1A, and those reaching sCr and UO criteria with increased BM are reclassified as Stage 1B. BM positivity should be based on its mechanism and defined threshold. * Source: Acute Disease Quality Initiative 23 (www.adqi.org).

Figure 2. Damage biomarker versus functional decrease matrix



+ = positive; – = negative; AKI = acute kidney injury; BM = biomarker; sCr = serum creatinine; UO = urine output. Patients with a BM of injury positivity without increase (or decline) in sCr level and not reaching UO criteria should be classified as Stage 1S. Reassessment is recommended according to clinical context and temporal trends. Patients reaching sCr and UO criteria with no increase on BM are defined as Stage 1A, and those reaching sCr and UO criteria with increased BM are reclassified as Stage 1B. BM positivity should be based on its mechanism and defined threshold. * Source: Acute Disease Quality Initiative 23 (www.adqi.org).

were obtained by implementing a KDIGO-recommended intervention after triaging with urinary [TIMP-2]·[IGFBP7] following major non-cardiac surgery, achieving a 66% reduction in Stage 2 and Stage 3 AKI as well as a 5-day reduction in length of stay and associated health care costs.[28]

Combining damage biomarkers with functional biomarkers also improves diagnostic precision and management of AKI. For example, in children after cardiopulmonary bypass using plasma cystatin C (pCysC) as the functional biomarker and urinary NGAL (uNGAL) as the damage biomarker, the composite uNGAL+/pCysC+ demonstrated a greater likelihood than an increase in creatinine for severe AKI (Stage 2/3) and for persistent AKI (lasting > 48 hours).[16]

However, some refinements were needed to align such a combined function-damage biomarker definition with the three consensus severity stages agreed under the current KDIGO umbrella. Appropriate alignments were proposed at the 23rd Acute Dialysis Quality Initiative (ADQI) meeting in 2019 (www.adqi.org)[29] wherein each functional AKI stage is subclassified into BM+ and BM– stages (Figure 1 and Figure 2).

Other subphenotypes (also called endophenotypes) may be definable based on the particular biomarker and clinical scenario.[30]

What is lacking now is the widespread dissemination of both information and practice in the clinical arena. It is easy to highlight that much more research is needed. This comes with the territory of introducing new methodologies. However, the time is ripe to introduce biomarkers into hospital clinical practice. A guided and restricted scenario experience will familiarise clinicians with the appropriate use of kidney damage biomarkers, while containing unnecessary costs. This approach is exactly the way the use of creatinine kinase and, subsequently, troponins have facilitated both better biomarkers and better biomarker utilisation in diagnosis and management of myocardial infarction.

Therefore, we recommend initial implementation of biomarkers in high risk settings while clinical familiarity increases. Ideally, a panel of biomarkers should be used, wherein biomarkers with different time courses and mechanisms of release are present, so that the performance of individual biomarkers can be evaluated in different clinical contexts. Realistically, NGAL and [TIMP-2]·[IGFBP7] should constitute such a panel until more validated biomarkers for hospital laboratory platforms are commercially available. These should be adequate for initial clinical experience in major high risk settings, as these two biomarkers have distinct profiles. [TIMP-2]·[IGFBP7] is a stress biomarker with a relatively short duration of increase after an injury, while

longer and continuing damage will increase both urinary and plasma NGAL. In addition, the already available AKI biomarkers of urinary albumin and urine microscopy for casts would complement this AKI panel.

However, there is a caveat: damage biomarkers are imperfect, just like serum creatinine. Both are an "aid to" rather than a substitute for clinical judgement. Nevertheless, only through hands-on clinical experience in realistic clinical settings will damage biomarkers begin to enhance clinical practice in the same way that the evolution of cardiac injury biomarkers has led to earlier diagnosis of myocardial infarction, early and successful intervention and, through greater awareness of need, to even better biomarkers.

Competing interests

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