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EDITORIAL

# Biomarker of persistent acute kidney injury: another gemstone in the jewelry box

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Acute kidney injury (AKI) is a very common complication of acute illnesses and is associated with poor short- and long-term outcomes [1, 2]. The intensity and timeline of AKI development and recovery can impact these outcomes. Indeed, compared with transient AKI (lasting less than 48 h), persistent AKI (lasting > 48 h and < 7 days) and acute kidney disease (AKD; lasting between 7 and 90 days) are known to be associated with higher mortality and morbidity including *de novo* or progressive chronic kidney disease [3, 4]. Hence, early identification of patients at risk of persistent AKI and AKD might promote secondary and tertiary preventive measures to improve patient outcomes, respectively (Fig. 1) [5].

While serum creatinine is generally recognized to be a poor biomarker of timely AKI detection in critically ill patients [6], many biomarkers have been developed in recent years with the hope of finding an earlier, more sensitive predictor of AKI. These biomarkers could potentially provide means for early, AKI-specific, pathophysiology-dependent, non-expensive prediction, with rapid turnaround time, and the potential ability to predict the impact of therapeutic measures and outcomes. Unfortunately, the majority of these biomarkers failed to fulfill these expectations [7]. A combination of tissue inhibitor metalloproteinase-2 ($TIMP_2$) and insulin-like growth factor-binding protein-7 ($IGFBP_7$) seems to be a promising new addition to the current biomarkers with potential for clinical and investigative utility [8–11]. While this combination has a very high performance in predicting the risk of AKI, in a recent study, these biomarkers were found to have limited ability to predict kidney recovery after an episode of AKI [12].

Modifications of the AKI clinical course may be achievable by biomarker-guided timely adjustment of disease-modifying, patient-specific interventions according to Kidney Disease: Improving Global Outcomes (KDIGO) bundle [13]. Biomarkers enabling the early identification of renal recovery are eagerly expected by the medical community as their application would potentially impact the long-term burden of severe and prolonged AKI for patients and healthcare systems. In a recent observation [3], five evolutionary patterns of stages 2 and 3 of AKI were described. In only one-fourth of patients, AKI reversal was complete or near-complete within 7 days, another fourth did not recover, about 10% had a late reversal, and the remaining patients relapsed after AKI reversal, with (22%) or without (15%) ultimate recovery. The absence of early reversal or presence of relapse in AKI impacts the outcomes in each phenotype considerably. Anticipating which patients end in each sub-phenotype is challenging. Therefore, at this juncture in the history of progress in the management of patients with AKI, understanding and predicting the nature of kidney injury recovery appears as important as timely detecting or predicting AKI occurrence. This could particularly impact the decision-making processes (e.g., renal replacement therapy -RRT- initiation, admission to intensive care unit), which potentially affects patients' outcomes and cost of care.

Currently, there are only a few studies exploring the prediction of kidney injury intensity or recovery. Bhatraju and coworkers [14] found that the serum creatinine level trajectory, in the first 72 h of injury, may identify patients with different risk of death, regardless of AKI severity. Unfortunately, 72 h of serum creatinine trending may be prohibitive to identify higher-risk patients early enough for the implementation of appropriate intervention. A recent meta-analysis by Klein and co-workers [15]

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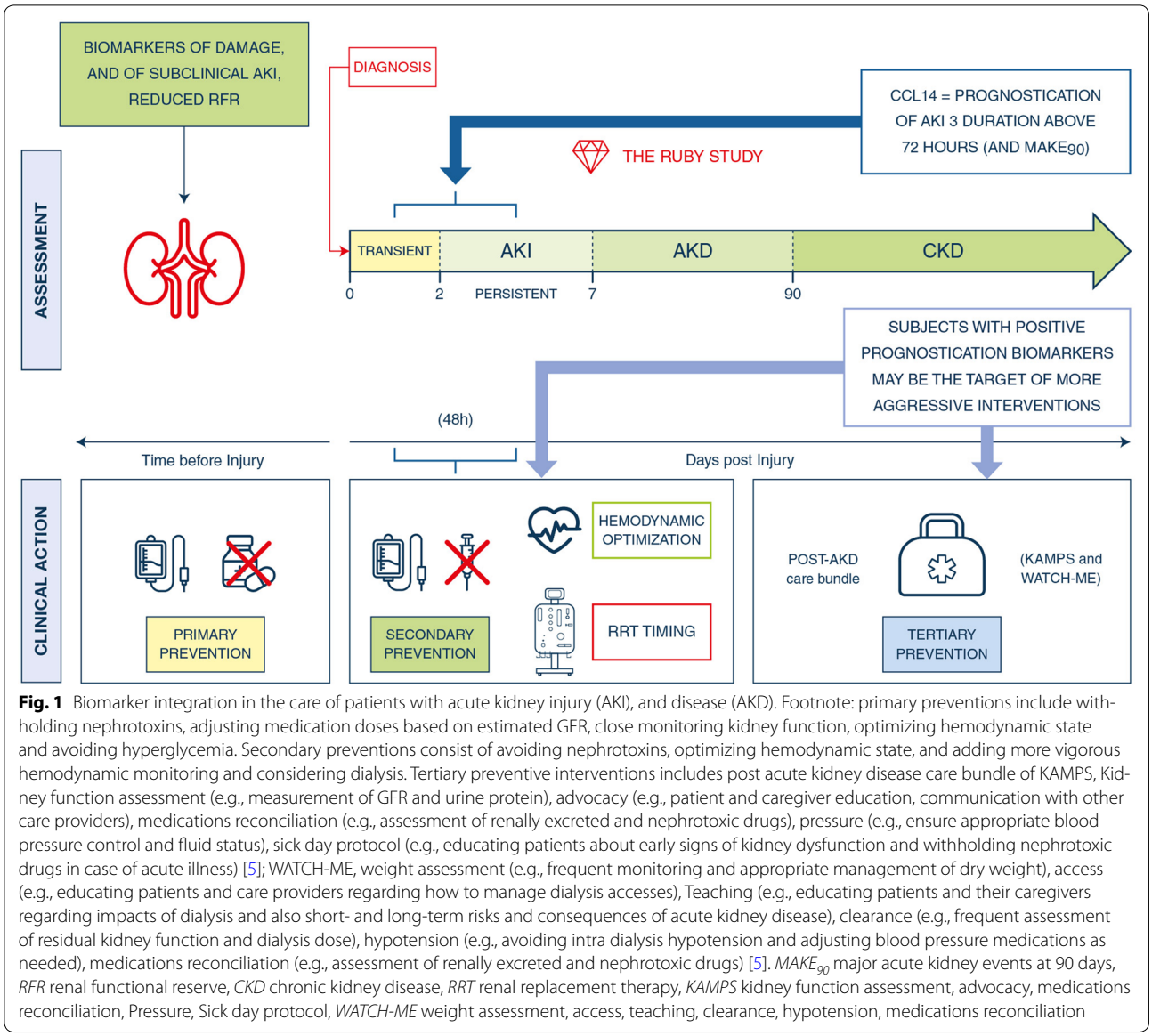


**Fig. 1** Biomarker integration in the care of patients with acute kidney injury (AKI), and disease (AKD). Footnote: primary preventions include withholding nephrotoxins, adjusting medication doses based on estimated GFR, close monitoring kidney function, optimizing hemodynamic state and avoiding hyperglycemia. Secondary preventions consist of avoiding nephrotoxins, optimizing hemodynamic state, and adding more vigorous hemodynamic monitoring and considering dialysis. Tertiary preventive interventions includes post acute kidney disease care bundle of KAMPS, Kidney function assessment (e.g., measurement of GFR and urine protein), advocacy (e.g., patient and caregiver education, communication with other care providers), medications reconciliation (e.g., assessment of renally excreted and nephrotoxic drugs), pressure (e.g., ensure appropriate blood pressure control and fluid status), sick day protocol (e.g., educating patients about early signs of kidney dysfunction and withholding nephrotoxic drugs in case of acute illness) [5]; WATCH-ME, weight assessment (e.g., frequent monitoring and appropriate management of dry weight), access (e.g., educating patients and care providers regarding how to manage dialysis accesses), Teaching (e.g., educating patients and their caregivers regarding impacts of dialysis and also short- and long-term risks and consequences of acute kidney disease), clearance (e.g., frequent assessment of residual kidney function and dialysis dose), hypotension (e.g., avoiding intra dialysis hypotension and adjusting blood pressure medications as needed), medications reconciliation (e.g., assessment of renally excreted and nephrotoxic drugs) [5]. *$MAKE_{90}$* major acute kidney events at 90 days, *RFR* renal functional reserve, *CKD* chronic kidney disease, *RRT* renal replacement therapy, *KAMPS* kidney function assessment, advocacy, medications reconciliation, Pressure, Sick day protocol, *WATCH-ME* weight assessment, access, teaching, clearance, hypotension, medications reconciliation

concluded that while some biomarkers are promising, their routine use to guide decision-making regarding the time of RRT initiation could not be recommended. In a recent small prospective study, Garnier and coworkers found that renal resistive index, but not $TIMP_2$-$IGFBP_7$, performed reasonably well in predicting persistent AKI in unselected critically ill patients with AKI [12].

In the present issue of Intensive Care Medicine, Hoste et al. reported the results of the Ruby trial which is a prospective observational multicenter and international study in 331 patients with AKI stages II and III to describe the discovery and validation of potential biomarkers identifying patients with persistent, severe AKI (stage 3), lasting for 72 h or more [16]. The investigators, among all measured potential biomarkers with a plausible relationship and pathophysiologic association with AKI persistence (i.e., apoptosis, necrosis, endothelial injury, cell–cell and cell–matrix adhesion, cytoprotection, oxidative processes, cell-cycle regulation, inflammation, tubular injury, immune function, and fibrosis), found urinary C–C motif chemokine ligand 14 (CCL14) to have the highest ability to predict the primary outcome with area under the receiver operating characteristic curve of 0.83, outperforming other biomarkers of AKI persistence (i.e., urinary $Chitinase_3$-$Like_1$, plasma cystatin C, plasma proenkephalin, urinary neutrophil gelatinase-associated lipocalin, and urinary liver fatty acid-binding protein). They also found a dose–response relationship between the urinary CCL14 levels and major adverse kidney events, a composite of death, dialysis, persistent decline in kidney function, at 90 days ($MAKE_{90}$). More importantly,

they noted that the use of CCL14 improves the performance of a clinical risk prediction model in identifying patients with persistent AKI.

This very well-conducted study provides important insights related to AKI. First, by highlighting the importance of inflammation in the persistence of AKI, it sheds valuable light on the pathophysiology of the natural course of severe AKI evolution, particularly the role of monocytes/macrophages recruitment. This may lead to further studies to develop and validate the effect of medications or interventions to modify monocytes/macrophages function as therapeutic targets. In addition, it provides a new tool for prediction of persistent kidney dysfunction beyond clinical estimation, which could improve AKI prognostication and severity stratification, or guide the decision-making processes related to the level of care adjudication and need for follow-up, or the timing of RRT initiation. Although patients enrolled in the RUBY trial were from multiple centers, it must be acknowledged that the variability of patients with different AKI etiologies and subcategories was rather low. This may impact the generalizability of the findings of the RUBY trial. However, if the performance of CCL14 is confirmed in other independent prospective studies in unselected critically ill individuals and/or specific cohorts of patients, it is expected to become an important tool in the contemporary management of AKI.

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**Compliance with ethical standards**

**Conflicts of interest**
AS, ZR, and KK have no conflict of interest to disclose.

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