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EDITORIAL

Persistent severe AKI is bad—where to go now?

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Two decades of careful iterative development by dedicated intensivists, nephrologists and statisticians, defining then refining acute kidney injury (AKI), and finally evaluating these definitions against clinical data confirm what we feared: namely that AKI is bad. It is not only bad but often leads to chronic kidney disease (CKD). The more severe the AKI, the poorer the survival. Not only the degree of function loss, visualised until recently as the extent of plasma creatinine concentration increase but also the duration of AKI is a marker of severity.

Duration of AKI was first clearly identified as important after cardiac surgery, where longer duration AKI was associated with worse long-term survival regardless of whether recovery occurred [1]. Experts of the 16th Acute Disease Quality Initiative meeting clarified the terminology with AKI duration defined as 'transient' and 'persistent' using recovery within 48 h as the time frame and further defined persistence beyond 7 days as acute kidney disease (AKD) [2]. Subsequently, the criteria of AKD were harmonized by KDIGO (Kidney Disease: Improving Global Outcomes) as acute kidney dysfunction lasting from onset up to 90 days [3]. Renal recovery itself remains controversial with uncertainty regarding the extent of preservation of kidney functional reserve. Clearly, the terminology must continue to evolve with improvements in understanding.

The retrospective cohort study in critically ill adults of Gomez and colleagues identified AKI during stay in the Intensive Care Unit (ICU) in 96,591 subjects (out of 190,550 encounters), 65,119 of whom had AKI KDIGO stage 2 or 3, and of these 8059 (12.4%), or 4.2% of first encounters of the total (190,550) critically ill cohort, progressed to 'persistent severe AKI', defined as AKI KDIGO stage 3 lasting for ≥ 72 h [4]. As anticipated, patients with persistent severe AKI were at higher risk of in-hospital mortality [HR = 2.21, 95% confidence interval (CI) 2.06, 2.38] and 90-day mortality (HR = 1.49, 95% CI 1.42, 1.56), and had a lower probability of recovery compared to those with AKI KDIGO stage 2 or 3 and resolution prior to 72 h. Risk factors for persistent severe AKI as compared with non-persistent severe AKI included severity of first AKI occurrence, community-acquired AKI, high positive fluid balance, multiple organ dysfunction, sepsis and shock.

The results can be summarized as: the more severe the AKI, the worse the prognosis, the longer it lasts, the worse the prognosis for both renal and patient recovery. These conclusions support two extensive earlier analyses [5, 6]. Ozrazgat- Baslanti et al. evaluated AKI trajectories in 156,699 hospitalized patients, including one-year follow-up after discharge and demonstrated that patients with transient AKI—a rapidly reversed rise in creatinine within 48 h—had much better outcomes than those with persistent AKI, defined as AKI lasting longer than 48 h [5]. The study also demonstrated that subjects who recovered from persistent AKI had an improved survival. Similarly, a study of 169,582 patients with AKI in Denmark showed after 20-year follow-up, that the longer AKI lasted, the greater the risk of CKD: with 20-year risks of CKD of 26.3%, 29.5%, and 28.7% for rapid reversal AKI, persistent AKI, and AKD, respectively [6].

While the two earlier studies focused on longer-term follow-up, the work of Gomez and colleagues explored in-hospital and 90-day mortality and utilised information from AKI experienced during the whole of the ICU

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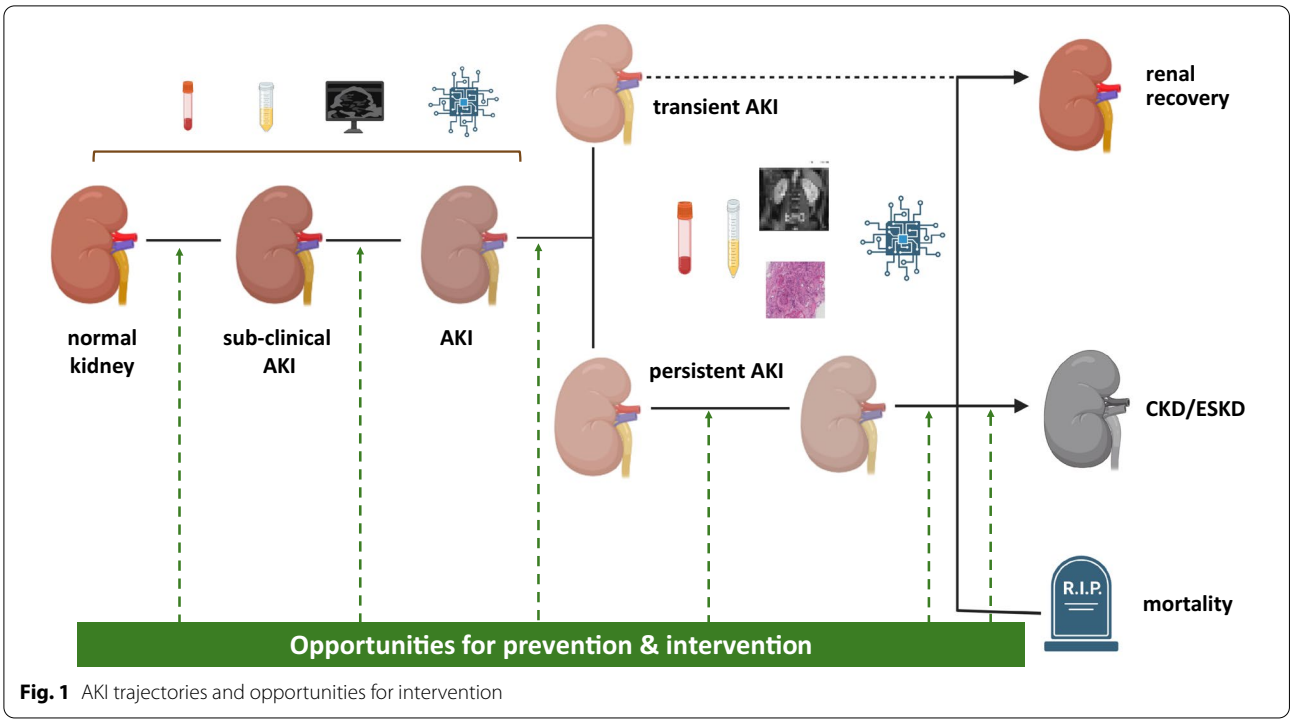

Fig. 1 AKI trajectories and opportunities for intervention

stay to classify patients at ICU admission. This leads to so-called immortal time bias where patients have to survive long enough to be categorized correctly [7, 8]. Given that classification into persistent AKI class is only possible after AKI has occurred and persisted for more than 72 h, the clock of the observation period should start afterwards.

To overcome immortal time bias, the authors performed several sensitivity analyses. They used a landmark approach, in which only subjects who survived until landmark time were analyzed, and they also set the time origin to 72 h after the first occurrence of stage 2–3 AKI. Although hazard ratio estimates varied in different sensitivity analyses (hazard ratios from 1.14 to 1.55), the results consistently showed a higher risk of mortality in patients with persistent severe AKI. A model acknowledging the time-dependency of AKI status and considering the time of persistence could improve understanding of persistent AKI and its association with outcome further [9].

Nevertheless, we need to move beyond confirming what we already know. What does defining persistent severe AKI tell us? Does it guide management or identify treatment targets? The repeated failure of intervention trials that target severe AKI has been endlessly explored. Clearly, most should not be repeated, such as utilising interventions for established AKI based on successful treatments given at the time of initiation of experimental AKI. *And clearly, if creatinine is used to define AKI, then all AKI is well established!*

Firstly, we know that supportive care is all that is available for syndrome management, whether that syndrome is AKI, acute coronary syndrome or acute respiratory distress syndrome or anything else. Consequently, our first priority should be to define the cause and mechanism of AKI—identification of subphenotypes and endotypes is needed over and above defining the syndrome [10, 11]. Biomarkers (including imaging and early kidney biopsy) may help with this and allow differentiation of AKI types and matching specific interventions to individual diseases [12] (Fig. 1).

Secondly, we suggest that directing the focus onto early, milder not late, severe AKI may have more success in prevention and treatment strategies. While controversial, eAlerts combined with a care bundle have reduced the length of hospital stay in stage 1 AKI in at least one study [13] but the data are not consistent. Apart from eAlerts, we now have better and more timely markers of kidney function change, including cystatin C and proenkephalin, and commercial biomarkers of kidney damage are available that can confirm renal injury in a timely fashion, including NGAL, cell cycle arrest markers, L-FABP, KIM-1 and C–C motif chemokine ligand 14 (CCL14) [14]. The RUBY study identified CCL14 as the best predictor of persistent severe AKI, providing opportunities for early identification and potential intervention [15]. Furthermore, premarketing

approval has just been granted to MediBeacon by the Food and Drug Administration (FDA) for transdermal measurement of glomerular filtration rate (GFR) [16], offering the promise of real-time GFR measurement in critically ill patients, including recognition of progressive deterioration of renal function. Early biopsy should also be considered to improve the understanding of changes in human kidneys in early rather than late AKI [12] (Fig. 1).

We must support AKI management in stage 3, persistent AKI and we acknowledge the difficulties in providing this supportive as opposed to disease-specific care. However, we also know that the horse has bolted in stage 3, persistent AKI as illustrated again in this study by Gomez et al. Isn't it time we stopped the horse leaving the stable? Having new technologies at hand to identify high-risk patients mandates a search for strategies to achieve better patient-centered outcomes.

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Data availability
Data availability statement is not applicable.

Declarations

conflict of interest
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