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Critically Ill Definitions in Acute Kidney Injury Clinical Research

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Acute kidney injury (AKI) in the intensive care unit (ICU) is common, with reported incidences ranging from 6% to 57%, with sepsis as the most common etiology (19%–40% of the cases).[1] In both retrospective and prospective studies of ICU patients admitted with septic shock, the incidence of AKI ranged between 50% and 64% of patients and was associated with an odds ratio for 90-day mortality of 1.3 to 2.9 for patients with Kidney Disease Improving Global Outcomes stage 3 AKI compared with septic patients without AKI.[2] AKI requiring renal replacement therapy in these patients varies widely depending on the studied cohort. Long-term outcomes from a meta-analysis comparing patients with AKI versus without AKI at 6-month follow-up mirror those previously examined for in-hospital outcomes, with higher mortality rate, greater incident chronic kidney disease (CKD), and greater hemodialysis dependency.[3] Finally, there are incongruent results on the role CKD plays in the risk of AKI and outcomes in hospitalized patients in different cohorts.[4–6]

In this issue of *KI Reports*, the Acute Kidney Injury in Critical Illness Study Group[7] investigated the role underlying CKD plays in sepsis-related AKI in 90-day mortality and long-term renal outcomes. It was a single-center, retrospective cohort design including 6490 adult patients over a 5-year period. They reviewed 2632 adult patient charts of patients admitted to the ICU with severe sepsis or septic shock. Baseline CKD was determined by the most recent prehospitalization serum creatinine (sCr) (1–90 days before admission) and defined as Modification of Diet in Renal Disease estimated glomerular filtration rate <60 ml/min per 1.73 m^2. Patients without sCr measured during this preadmission time frame and patients with CKD-5 were excluded. AKI was determined by absolute and relative increases in creatinine comparing peak ICU sCr with baseline sCr. The 2 primary outcomes were mortality (defined as in-hospital and up to 90 days after discharge) and incident or progressive CKD (determined by mean of the 2 most recent sCr values in the chart at least 90 days after discharge). As expected, they found that severe AKI stage ≥ 2, regardless of underlying CKD, was associated with both higher mortality and greater incident or progressive CKD. Interestingly, they found that patients without underlying CKD had better outcomes than patients without underlying CKD for stage 1 AKI.

They are cautious not to overinterpret these results, given the limitations of retrospective cohort studies, but hypothesize that patients with baseline CKD and sCr-based stage 1 AKI may have less intrinsic damage compared with patients with stage 1 AKI without baseline CKD. One interpretation of their findings is a high false-positive rate of stage 1 AKI in patients with CKD due to clinically insignificant fluctuations in sCr in this group[8]; however, there were no significant differences in their sensitivity analysis comparing relative versus absolute changes in sCr in this group. One alternative explanation they propose is that decreased renal reserve seen in CKD results in more apparent rises in sCr following transient hypoperfusion compared with a similar hypoperfusion injury in patients with greater renal reserve, which masks the true extent of the injury. The authors also entertain the possibility of low renal mass contributing to a preconditioned state that allows patients with CKD to be more resilient to insults compared to patients without baseline CKD.

As previously discussed, there are contradictory studies in this field,[4–6] and although this study addresses an important question examining the role that underlying CKD has on the relative risk of adverse outcomes following AKI, it generates more questions than definitive answers. The investigators propose plausible

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explanations for their findings, and they recognize the limitations of these explanations by highlighting the need for prospective clinical studies with detailed subtyping of AKI not only by severity but also by duration and using biomarkers beyond just sCr.

In addition to addressing the important clinical question of the interplay among sepsis, CKD, and AKI, the strengths and limitations of this study also highlight the current challenges in AKI clinical research.

Their definition of baseline CKD was limited by the use of the Modification of Diet in Renal Disease, which may have misclassified patients into the CKD group (estimated glomerular filtration rate <60) by underestimating the estimated glomerular filtration rate. Similarly, relying on a single prehospitalization sCr may also misclassify patients and reflects a difference in methodology in their determination of baseline CKD versus incident or progressive CKD, in which the mean of 2 values was used. A major strength was their decision not to use admission sCr to determine baseline CKD status; however, excluding the 7 days before admission has been shown to be the most reliable method for determining baseline estimated glomerular filtration rate.[9]

Although they cite Kidney Disease Improving Global Outcomes sCr-based criteria for defining AKI, they diverge from these criteria by comparing peak sCr during the ICU admission with baseline sCr rather than a percentage change from baseline, or an absolute change within a 48-hour period. This is further complicated by the use of ICU admission Sequential Organ Failure Assessment rather than Sequential Organ Failure Assessment scores immediately before the AKI event. Although using peak sCr leads to higher incidence reporting and is an easier method to analyze, it introduces important and significant biases when trying to compare it with an event without reporting the temporal relationship to the AKI episode.

Retrospective cohorts have several important limitations when determining outcomes. One of the greatest limitations of their findings was the heterogeneity in the definition of their primary outcome. They defined mortality as in-hospital mortality *or* mortality 90 days after discharge (not 90 days after the AKI event). The determination of incident or progressive CKD was also not constrained, and they used the mean of the 2 most recent sCr values, which resulted in a median follow-up period of 15.3 months, with a very wide interquartile range of 5.7 to 29.2 months. Further complicating these results is the significant attrition, as only 64% of the ICU survivors had follow-up sCr available beyond 90 days, which remains a common challenge in outcomes-based clinical research.

Their work adds to the conversation of the role baseline CKD plays in the mortality of patients with CKD who develop AKI, and highlights the challenges in this field with standardizing definitions. Although there are methodologic limitations to their outcomes, it is refreshing to see such transparency in the exact definitions of determining baseline CKD, sCr-based AKI definitions, and CKD outcomes. Although many studies cite "Kidney Disease Improving Global Outcomes Criteria," there are many nuances, variations, and departures from the standardized definitions that remain opaque in most methods sections and this introduces important biases, limits generalizability, and makes it challenging to compare findings from different studies. Although absolute standardization of methods is challenging due to available data in different study cohorts, the very least we can do as a community is hold authors accountable for being transparent in reporting the exact details of their determination of baseline renal function, scoring of AKI, and definition of outcomes in their methods section, as Neyra *et al.*[7] have done in this study.

DISCLOSURE

The author declared no competing interests.

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