Critically Ill Definitions in Acute Kidney Injury Clinical Research

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See Clinical Research on Page 1344

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 of 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 Group7 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 m². Patients without sCr measured during this predmission 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 group8; 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
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 Mod-
ification of Diet in Renal Disease,
which may have misclassified pa-
tients 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; how-
ever, 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 Dis-
ease 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 Assess-
ment 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 find-
ings 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 determi-
nation 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 clini-
cal research.

Their work adds to the conversa-
tion of the role baseline CKD plays in
the mortality of patients with CKD
who develop AKI, and highlights the
challenges in this field with stan-
dardizing definitions. Although
there are methodologic limitations to
their outcomes, it is refreshing to see
such transparency in the exact defi-
nitions 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 de-
partures from the standardized defi-
nitions that remain opaque in most
methods sections and this introduces
important biases, limits generaliz-
ability, and makes it challenging to
compare findings from different
studies. Although absolute stan-
dardization of methods is chal-
lenging 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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