Underscoring the Case for Better Markers of Kidney Injury in Deceased Donors

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Deceased organ donors frequently have acute kidney injury (AKI), which results in elevated terminal creatinine. The elevated terminal creatinine, rather than the baseline creatinine, is used to calculate the Kidney Donor Profile Index (KDPI), which results in a higher KDPI percentile when a donor experiences AKI. This high KDPI further disadvantages organs with AKI, which are already at a disproportionately increased risk of discard secondary to concerns for delayed graft function (DGF) and allograft failure in recipients. Observational national registry data from the United States and Australia have demonstrated a consistent association of donor AKI with DGF but not with longer-term allograft function, a finding that has been replicated repeatedly in multiple single-center studies and systematic reviews. Although many of these studies were potentially limited by their use of terminal creatinine, these relationships are unchanged by more granular phenotyping using sequential creatinine values or histological evidence of acute tubular necrosis.

In this issue of AJKD, Lenain et al report on the association of donor AKI with subsequent allograft outcomes in the French national transplant registry by adding a twist to the definition of AKI. As a true baseline creatinine is not available in deceased donors, they imputed the donors’ baseline estimated glomerular filtration rates (eGFRs) and then used these values to calculate baseline serum creatinine and to subsequently define AKI in the deceased donors. Although this is a novel approach to determine if a deceased donor experienced AKI, this strategy has been previously used in epidemiological studies of AKI in native (nontransplanted) kidneys when a baseline creatinine value is unavailable. The results of this study are particularly notable, as they suggest that grafts from donors who had AKI perform significantly worse but also are contrary to several prior studies suggesting otherwise. Compared with prior studies, this new approach for assessment of baseline creatinine also leads to a reduction of about 50% in the proportion of deceased donors deemed to have had AKI at the time of procurement.

The use of a back-calculated creatinine from a presumed baseline eGFR is not without challenges. As Lenain et al so elegantly demonstrate with Sankey diagrams, the reclassification of donors with and without AKI results from the introduction of a presumed baseline across their different phenotypes. To what extent this reclassification resulted in inadvertent enrichment of subcohorts with kidneys from donors with suboptimal characteristics is a complex question and a likely contributor to the observed results.

These thought-provoking findings raise several important questions with implications that are unclear, particularly for the US allocation system, which has the highest discard rate in the world. Compared with the system in the United States, deceased donor allocation in France uses kidneys from significantly older donors with a much higher mean Kidney Donor Risk Index (KDRI) but lower serum creatinine concentrations. The discard rate in France is approximately one-half that seen in the United States, but primary nonfunction or early graft failure rates in France are 4- to 6-fold higher. Furthermore, procurement biopsies, although of limited utility because of concerns about reproducibility and reliability, are incorporated into the organ offer acceptance decision in the United States but are unavailable in France at the time of the organ offer. These differences in the systems and in the information available to inform organ acceptance decisions probably result in different selection biases, thus creating differences in the kidneys being used as well as differences in the patients for whom these kidneys are eventually accepted. Procurement biopsies have significant limitations in terms of reliability and reproducibility, which calls into question their value in informing organ acceptance decisions, particularly when there appears to be a lack of association between histology and longer-term outcomes. Despite this, many centers continue to rely extensively on procurement biopsy findings, particularly in instances of an elevated terminal creatinine, purportedly to distinguish AKI from more chronic forms of injury—a practice that is highly variable across the country and one that is without clear evidence that it leads to better organ offer decisions.

We should note that although the differences in allograft outcomes with kidneys from donors with AKI are statistically significant, even in this analysis they are not meaningfully different from a clinical perspective. This is especially true given that the alternative to using these kidneys is for patients to remain on dialysis, which portends a dramatically lower patient survival—a point that is also made by the authors. We can gain additional context from the fact that the worst outcomes were seen with AKI stage 2 kidneys, with an adjusted hazard ratio of 1.37 (95% CI, 1.16-1.63) compared to patient without AKI. In addition, stage 3 AKI kidneys did not have increased risk of graft failure in this analysis. Kidneys from donors carrying the apolipoprotein L1 (APOL1) risk alleles have an adjusted hazard ratio >2, but no one would suggest that kidneys from donors carrying 2 APOL1 risk variants should not be
used. In other words, the identification of a statistically significant relative risk in this instance does not appear to represent a clinically meaningful absolute difference.

The takeaway message from this thought-provoking study remains in question. Although imputation of data can be justified for large cohorts to aid in statistical analyses, clinicians are compelled to use the available data while remaining cognizant of the diagnostic uncertainty that results from missing baseline data. Given that missing data, particularly baseline data, is a common clinical reality, it seems unlikely that clinicians will use baseline defaults or estimates in the evaluation of individual organ offers. It should also be noted that AKI reclassification using imputed creatinine data is likely to be different in different cohorts. For example, in the United States, where the average age of deceased donors is much lower, the use of this approach would actually classify donors differently—but whether this would encourage the use of deceased donor organs is difficult to predict.

Although it is unlikely that these analyses will inform organ offer decisions, especially in the United States, they clearly underscore the limitations of creatinine as a measure of kidney function and injury. We should also note that currently available AKI injury biomarkers, such as L-FABP (liver-type fatty acid binding protein), IL-18 (interleukin 18), and KIM-1 (kidney injury molecule 1), perform relatively poorly when used to identify acute tubular injury, whereas urinary NGAL (neutrophil gelatinase-associated lipocalin) performs only marginally better. Repair markers such as YKL-40 (chitinase-3-like gelatinase-associated lipocalin) performs only marginally better when used to identify acute tubular injury, whereas urinary NGAL (neutrophil gelatinase-associated lipocalin) performs only marginally better. Repair markers such as YKL-40 (chitinase-3-like protein) appear able to identify deceased donor kidneys with AKI that are less likely to develop DGF and have improved longer-term kidney function. UMOD (uromodulin) and OPN (osteopontin) are proteins produced by the kidney that are frequently evaluated in settings of AKI because of their immunomodulatory properties and ability to regulate repair of injured cells. In a large, multicenter study, a UMOD:OPN ratio ≤3 in deceased donor urine was associated with reduced death-censored graft failure, lower DGF, and higher 6-month kidney function in the recipients.

These findings underscore the need for more research on how to use currently available repair biomarkers to help phenotype deceased donor kidneys with AKI while also searching for new markers that might help assess organ quality. The availability of such biomarkers as point-of-care measurements will reduce dependence on creatinine-based AKI definitions and their attendant limitations. Improved assessments of kidney injury and repair in donors could inform clinical decisions about organ procurement, allocation, and utilization, which could culminate in lower organ discard rates without the unintentional consequences of increased primary nonfunction.

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