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Original Investigation

Performance of Serum Creatinine and Kidney Injury Biomarkers for Diagnosing Histologic Acute Tubular Injury

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Background: The diagnosis of acute kidney injury (AKI), which is currently defined as an increase in serum creatinine (Scr) concentration, provides little information on the condition's actual cause. To improve phenotyping of AKI, many urinary biomarkers of tubular injury are being investigated. Because AKI cases are not frequently biopsied, the diagnostic accuracy of concentrations of Scr and urinary biomarkers for histologic acute tubular injury is unknown.

Study Design: Cross-sectional analysis from multicenter prospective cohort.

Settings & Participants: Hospitalized deceased kidney donors on whom kidney biopsies were performed at the time of organ procurement for histologic evaluation.

Predictors: (1) AKI diagnosed by change in Scr concentration during donor hospitalization and (2) concentrations of urinary biomarkers (neutrophil gelatinase-associated lipocalin [NGAL], liver-type fatty acid-binding protein [L-FABP], interleukin 18 [IL-18], and kidney injury molecule 1 [KIM-1]) measured at organ procurement.

Outcome: Histologic acute tubular injury.

Results: Of 581 donors, 98 (17%) had mild acute tubular injury and 57 (10%) had severe acute tubular injury. Overall, Scr-based AKI had poor diagnostic performance for identifying histologic acute tubular injury and 49% of donors with severe acute tubular injury did not have AKI. The area under the receiver operating characteristic curve (AUROC) of change in Scr concentration for diagnosing severe acute tubular injury was 0.58 (95% CI, 0.49-0.67) and for any acute tubular injury was 0.52 (95% CI, 0.45-0.58). Compared with Scr concentration, NGAL concentration demonstrated higher AUROC for diagnosing both severe acute tubular injury (0.67; 95% CI, 0.60-0.74; $P = 0.03$) and any acute tubular injury (0.60; 95% CI, 0.55-0.66; $P = 0.005$). In donors who did not have Scr-based AKI, NGAL concentrations were higher with increasing severities of acute tubular injury (subclinical AKI). However, compared with Scr concentration, AUROCs for acute tubular injury diagnosis were not significantly higher for urinary L-FABP, IL-18, or KIM-1.

Limitations: The spectrum of AKI cause in deceased donors may be different from that of a general hospitalized population.

Conclusions: Concentrations of Scr and kidney injury biomarkers (L-FABP, IL-18, and KIM-1) lack accuracy for diagnosing acute tubular injury in hospitalized deceased donors. Although urinary NGAL concentration had slightly higher discrimination for acute tubular injury than did Scr concentration, its overall AUROC was still modest.

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INDEX WORDS: Acute kidney injury (AKI); acute tubular injury (ATI); serum creatinine (Scr); NGAL; L-FABP; KIM-1; IL-18; kidney biopsy; kidney histology; subclinical AKI; kidney injury biomarker; diagnostic performance.

Clinically, acute kidney injury (AKI) is defined by an increase in concentration of serum creatinine (Scr), which is a marker of glomerular filtration rate (GFR), or by acute reductions in urine output. Acute tubular injury is frequently presumed to be a leading cause of AKI in many hospital settings.[1,2] Acute tubular injury is a histologically diagnosed condition and is often associated with

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progressive chronic kidney disease (CKD) and end-stage renal disease.[3,4]

Scr-based AKI definitions have several limitations when applied to diagnose acute tubular injury.[5] First, elevations in Scr concentrations are not specific to acute tubular injury. Administration of drugs that inhibit tubular secretion of creatinine or inhibit the renin-angiotensin-aldosterone system can lead to increases in Scr concentrations in the absence of acute tubular injury. Hemodynamic reductions in renal blood flow that do not cause structural injury but increase Scr concentrations can also lead to false-positive acute tubular injury diagnoses (eg, cardiorenal and hepatorenal syndromes).[5-7] Second, Scr concentration can fail to identify some patients who have acute tubular injury, a condition termed "subclinical AKI."[8,9] This can occur when the effects of tubular injury and reduced GFR in some nephrons are compensated for by other noninjured and functioning nephrons via a phenomenon called "renal reserve." Although many investigators and clinicians recognize the limitations of Scr concentration and would prefer a kidney biopsy to confirm acute tubular injury, patients with suspected acute tubular injury are frequently critically ill and thus rarely undergo biopsy. Instead, other clinical parameters such as fractional excretion of sodium, fractional excretion of urea, serum urea nitrogen (SUN) to Scr (SUN:SCr) ratio, urine output, and urine microscopy are used in conjunction with elevations in Scr concentration to infer the diagnosis of acute tubular injury.

Translational researchers are evaluating urinary proteins that directly assess tubular injury for noninvasive confirmation of acute tubular injury. Protein biomarkers currently under consideration include neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), interleukin 18 (IL-18), and kidney injury molecule 1 (KIM-1). However, despite the limitations of Scr concentration, studies of these biomarkers have used Scr concentration for comparison rather than the gold standard of kidney biopsy–diagnosed acute tubular injury.[10] This has led to suboptimal biomarker development.[5]

Acute tubular injury is common in deceased organ transplant donors,[11] who are managed in the intensive care unit before organ procurement.[12] Donor management involves the same critical care provided to other intensive care unit patients. The cause of and risk factors for AKI in deceased donors are thus similar to those of other intensive care unit patients.[13] Moreover, organ procurement clinicians perform kidney biopsies in more than half these donors, and biopsies are often used to help make organ allocation decisions. Thus, the deceased donor setting provides an opportunity to compare urinary tubular injury biomarkers with Scr for acute tubular injury confirmed via gold-standard histology.

We hypothesized that urinary biomarkers of kidney injury would have improved discrimination for diagnosing histologic acute tubular injury compared to Scr concentration. In a prospective multicenter cohort of deceased organ donors with kidney biopsies performed at the time of organ procurement for transplantation, we compared the accuracy of urinary tubular injury biomarkers (NGAL, L-FABP, IL-18, and KIM-1) with traditional clinical parameters (Scr, fractional excretion of sodium, fractional excretion of urea, SUN:Scr ratio, and urine output) for diagnosing histologic acute tubular injury.

METHODS

Study Design

We have previously described the details of this multicenter prospective cohort of deceased kidney donors.[14,15] Briefly, we collaborated with 5 organ procurement organizations (OPOs). These OPOs collected donor urine samples as per study protocol at the time of organ procurement between April 2010 and November 2013 from donors whose surrogates had given consent for research. In a subset of donors, the OPOs also obtained wedge biopsies of kidneys to assist with the allocation process. Frozen biopsy sections were reviewed by clinical pathologists at the respective hospitals or by pathologists contracted by the OPO. We excluded donors from this analysis if biopsies were not performed or biopsy reports did not mention either the presence or absence of acute tubular injury.

We obtained donor data from the Organ Procurement and Transplantation Network (OPTN) that were submitted by its members, which has been described elsewhere.[16] We reviewed OPO charts for additional donor information not available in the OPTN data system, including procurement kidney biopsy reports, admission donor Scr concentration, serum sodium concentration, SUN concentration, and urine output. In a subset of donors from each participating OPO, we also confirmed the quality and accuracy of OPTN data using these systematic chart reviews. We obtained recipient Scr values from the OPTN database, currently maintained under contract with the United Network for Organ Sharing (UNOS).

We adhered to the ethics principles of the Declaration of Helsinki and obtained institutional review board approval from the Data Coordinating Center at Yale (Human Research Protection Program Approval numbers: 0912006086, 0909005694, 0912006085, and 0909005696), as well as the respective institutional review boards and/or scientific review committees for all sites in the study. The clinical and research activities outlined here are also consistent with the principles outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.[17,18] We used deidentified UNOS data for recipient outcomes under an approved waiver of consent.

Exposures

We defined donor AKI as an increase in Scr concentration from admission to the terminal value (change in Scr) by $\geq$0.3 mg/dL or by $\geq$50% increase from baseline. Severe AKI was defined as $\geq$100% increase in Scr concentration. These Scr concentration cutoffs correspond to AKI Network (AKIN) stage 1 or greater and stage 2 or greater, respectively.[19,20] Because we did not have dates associated with the Scr concentration, we did not use KDIGO (Kidney Disease: Improving Global Outcomes) AKI definitions.