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Original Investigation

Urine Biomarkers and Perioperative Acute Kidney Injury: The Impact of Preoperative Estimated GFR

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Background: The interaction between baseline kidney function and the performance of biomarkers of acute kidney injury (AKI) on the development of AKI is unclear.

Study Design: Post hoc analysis of prospective cohort study.

Setting & Participants: The 1,219 TRIBE-AKI Consortium adult cardiac surgery cohort participants.

Predictor: Unadjusted postoperative urinary biomarkers of AKI measured within 6 hours of surgery.

Outcome: AKI was defined as AKI Network stage 1 (any AKI) or higher, as well as a doubling of serum creatinine level from the preoperative value or the need for post-operative dialysis (severe AKI).

Measurements: Stratified analyses by preoperative estimated glomerular filtration rate (eGFR) $\leq$ 60 versus $>$ 60 mL/min/1.73 m^2.

Results: 180 (42%) patients with preoperative eGFRs $\leq$ 60 mL/min/1.73 m^2 developed clinical AKI compared with 246 (31%) of those with eGFRs $>$ 60 mL/min/1.73 m^2 ($P < 0.001$). For $\log_2$-transformed biomarker concentrations, there was a significant interaction between any AKI and baseline eGFR for interleukin 18 ($P = 0.007$) and borderline significance for liver-type fatty acid binding protein ($P = 0.06$). For all biomarkers, the adjusted relative risk (RR) point estimates for the risk for any AKI were higher in those with elevated baseline eGFRs compared with those with eGFRs $\leq$ 60 mL/min/1.73 m^2. However, the difference in magnitude of these risks was low (adjusted RRs were 1.04 [95% CI, 0.99-1.09] and 1.11 [95% CI, 1.07-1.15] for those with preoperative eGFRs $\leq$ 60 mL/min/1.73 m^2 and those with higher eGFRs, respectively). Although no biomarker displayed an interaction for baseline eGFR and severe AKI, $\log_2$-transformed interleukin 18 and kidney injury molecule 1 had significant adjusted RRs for severe AKI in those with and without baseline eGFRs $\leq$ 60 mL/min/1.73 m^2.

Limitations: Limited numbers of patients with severe AKI and post-operative dialysis.

Conclusions: The association between early postoperative AKI urinary biomarkers and AKI is modified by preoperative eGFR. The degree of this modification and its impact on the biomarker-AKI association is small across biomarkers. Our findings suggest that distinct biomarker cutoffs for those with and without a preoperative eGFR $\leq$ 60 mL/min/1.73 m^2 is not necessary.

INDEX WORDS: Urine biomarkers; interleukin 18 (IL-18); liver-type fatty acid binding protein (L-FABP); acute renal failure (ARF); acute kidney injury (AKI); perioperative AKI; effect modification; estimated glomerular filtration rate (eGFR); prognosis; cardiac surgery; surgical complication.

Acute kidney injury (AKI) is the most common reason for inpatient nephrology consultation. Significant research efforts are focused on translating biomarkers of AKI so they become available for clinical use.[1,2] Although several urine biomarkers have demonstrated promise for their ability to detect AKI earlier than traditional markers or to predict disease progression, clinical factors that affect biomarker performance, such as decreased preoperative glomerular filtration rate (GFR), remain unclear.[3-6] Chronic kidney

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disease (CKD) as defined by decreased GFR is a common risk factor for the development of AKI, occurring in one-third to one-half of all those with AKI,[6-8] and is heavily weighted in a variety of AKI risk assessment tools.[9-11] Biomarkers such as urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) act as markers of renal tubular injury and as such, have recently been shown to be increased in the presence of CKD but absence of AKI.[12-15] However, when evaluated as a prognostic tool in the setting of AKI, these same markers have demonstrated varied performance in those with and without pre-existing decreased baseline GFRs.[16-18] It stands to reason that biomarker concentrations and kinetics will be different in those with and without decreased baseline GFRs because decreasing functional nephron mass and renal reserve will affect the kidney's ability to filter or produce these proteins. Additionally, if biomarker concentrations are higher in those with lower baseline GFRs, smaller renal insults resulting in phenotypically milder AKI (as evidenced by change in serum creatinine level) may lead to a disproportionate increase in biomarker concentration despite a weaker association with AKI. The interplay between AKI, GFR, and levels of urinary biomarkers of renal tubular injury remains unclear.

To clarify the interaction among urinary biomarker levels, GFR, and AKI, we performed a secondary analysis of the prospectively collected Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) adult cardiac surgery cohort to evaluate the effect modification by preoperative GFR on the association of 6 urinary biomarkers of AKI (NGAL, KIM-1, interleukin 18 [IL-18], liver-type fatty acid binding protein [L-FABP], cystatin C, and albumin), assessed in the hours following surgery, and AKI during the hospital stay.

METHODS

Patient Cohorts and Samples

Detailed methods of the TRIBE-AKI cardiac surgery cohort (ClinicalTrials.gov identifier NCT00774137) have been previously described.[6,19] Adults deemed high risk for AKI following cardiac surgery (coronary artery bypass grafting and/or valvular surgery) were prospectively enrolled at 6 academic medical centers in North America in July 2007 to December 2009. All participants provided written informed consent, and the study was approved by each institution's research ethics board. The first postoperative samples were collected within 6 hours of admission to the intensive care unit. For the first 24 hours postoperatively, urine samples were collected every 6 hours. The remaining daily blood and urine samples were obtained at the time of routine morning blood collection done for clinical care. Specimen collection was stopped on postoperative day 3 in patients who did not demonstrate AKI in the 3 days following surgery. Details for sample collection and processing have been previously described.[6,19]

Outcomes: Study Variables

The definition of AKI was the development, at a minimum, of a 50% increase or absolute increase of 0.3 mg/dL in serum creatinine level from the preoperative baseline during the hospital stay (AKI Network [AKIN] stage 1). Severe AKI was defined as developing at least a 100% increase in serum creatinine level from baseline or the need for renal replacement therapy.[20,21]

All preoperative creatinine and biomarker values were measured within 2 months before surgery. Pre- and postoperative serum creatinine concentrations were measured in the same clinical laboratory for each patient at all sites. Serum creatinine values were recorded for every patient throughout the hospital stay. For adults, we estimated preoperative GFR using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[22] As previously described, we collected preoperative characteristics, surgical details, and postoperative complications using definitions of the Society of Thoracic Surgeons.[6,19]

Biomarker Assays

All biomarkers were measured in blinded fashion with assay information and inter- and intra-assay coefficients of variation as previously described (Parikh et al[6] [IL-18 and NGAL], Parikh et al[23] [KIM-1 and L-FABP], Koyner et al[24] [cystatin C], and Molonar et al[25] [albumin]).

Statistical Analysis

Continuous variables were compared with a 2-sample t test or Wilcoxon rank sum test, and dichotomous variables, with χ^2 test or Fisher exact test. The adult population was divided into unique quintiles using the first postoperative value of each individual biomarker. Unadjusted trends across biomarker quintiles were assessed by Cochran-Armitage test for dichotomous outcomes. To evaluate the association between biomarkers and AKI, modified Poisson regression models with a log link function were used.[26] We adjusted for age, sex, race, history of hypertension, history of diabetes, history of congestive heart failure, surgery status (elective vs nonelective), type of surgery (bypass alone, valve alone, or bypass and valve), myocardial infarction, and cardiopulmonary bypass pump time. Biomarkers were included in models as $\log_2$-transformed continuous variables or as quintiles. To explore the possibility of effect modification by preoperative estimated GFR (eGFR), we included an interaction term in the model between eGFR $>$ 60 versus $\leq$60 mL/min/1.73 m^2 and the biomarker or CKD-EPI eGFR (continuously) and the biomarker. The same clinical adjustment variables were used across all analyses. All analyses were performed in SAS, version 9.2 (SAS Institute Inc), and R, version 2.12.1 (R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

Figure 1 provides information about TRIBE-AKI participants included in this analysis. Of 1,219 adults in the TRIBE-AKI cohort, 424 (34.8%) had a preoperative eGFR $\leq$ 60 mL/min/1.73 m^2.[22] Defined as AKIN stage 1, AKI occurred more commonly in those with preoperative eGFRs $\leq$ 60 mL/min/1.73 m^2: 180 of 424 (42.5%) compared with 246 of 795 (30.9%) in those without decreased baseline eGFRs ($P < 0.001$). Severe AKI, defined as AKIN stage 2 or higher, was not different in patients with and without decreased baseline GFRs ($P = 0.3$). Table 1 lists patient characteristics of those with and without preoperative