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Original Article

Combining Novel Renal Injury Markers with Delta Serum Creatinine Early after Cardiac Surgery and Risk-Stratification for Serious Adverse Outcomes: An Exploratory Analysis

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Objective: To evaluate the prognostic utility of multiple novel urinary biomarkers of renal injury when used alone, in pair-wise combination with an early delta serum creatinine (ΔS_{Cr}) term, and combined as a broad biomarker panel for the prediction of serious adverse outcomes that may reflect AKI in patients undergoing cardiac surgery.
Design: Post-hoc analysis of prospective observational study.
Setting: Academic medical center.
Participants: 603 adults undergoing cardiac surgery.
Interventions: None.
Measurements and Main Results: Urinary cystatin-c, kidney injury molecule-1, chemokine (C-C motif) ligand 2 and interleukin-18 were measured at baseline and <1 hour, 3 hours and 18-24 hours after separation from cardiopulmonary bypass (CPB). $\Delta S_{Cr\text{-initial}}$ was defined as the difference in S_{Cr} from baseline to first postoperative measure. The primary outcome of hospital mortality or renal replacement therapy occurred in 25 patients. Concordant elevation of any urinary biomarker measured 3 hours after CPB together with $\Delta S_{Cr\text{-initial}} \geq 0$ mg.dL^{-1} provided excellent early risk stratification for the primary outcome (OR ≥ 15.1, 95% CI 4.1-55.4). Combining four urinary biomarkers together with $\Delta S_{Cr\text{-initial}}$ and neutrophil gelatinase-associated lipocalin, previously reported from the same cohort, to provide a 6-point AKI risk score enabled early identification of patients reaching the primary outcome (ROC_{AUC} 0.86, 95% CI 0.79-0.92) with potentially useful sensitivity and specificity at varied cut-points.
Conclusions: Combining novel urinary biomarkers of renal injury with a creatinine-based metric soon after cardiac surgery provided excellent prognostic utility for serious adverse outcomes. Future studies are required to confirm these findings and determine optimal biomarker combinations for cost-effective risk stratification.

Key Words: acute kidney injury; biomarkers; thoracic surgery

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ACUTE KIDNEY INJURY (AKI) is a major complication after cardiac surgery, occurring in approximately 25% of patients and associated with a marked increase in serious morbidity and mortality.[1–4] The current lack of a reliable early diagnostic strategy prevents highly targeted early institution and evaluation of potential therapeutic strategies. Although development of novel renal injury biomarkers for the early recognition of AKI has been identified as a research priority[5] none have reliably and consistently provided early identification of a creatinine-based diagnosis of AKI after cardiac surgery. However, an acknowledged lack of sensitivity and specificity of serum creatinine (S_{Cr}) for true renal injury make it a poor end-point against which to validate novel biomarkers.[6] Rather, valid renal injury biomarkers should identify patients at increased risk of serious adverse outcomes that are a consequence of AKI.[7,8]

AKI is likely the end result of multiple pathophysiologic and molecular pathways, thus a single biomarker is unlikely to provide a comprehensive stand-alone diagnostic tool.[9,10] We have previously reported the prognostic utility of urinary neutrophil gelatinase-associated lipocalin (NGAL) when combined with a novel delta serum creatinine (ΔS_{Cr}) term within hours after adult cardiac surgery.[11] Using the same cohort for further exploratory analyses, the current study sought to evaluate the prognostic utility of four additional novel urinary biomarkers alone, in pair-wise combination with our previously reported early ΔS_{Cr} terms, and then combined into a broad biomarker panel to reflect increased activity across multiple potential pathophysiological pathways, for serious adverse clinical outcomes that may reflect AKI in a heterogenous cohort of adult patients undergoing cardiac surgery.

Materials and Methods

After Institutional Review Board (IRB) approval adult patients undergoing cardiac surgery between January 2010 and June 2011 were enrolled in a prospective observational study within a single academic medical center. In view of the minimal risk represented by collection of urine and routine perioperative data, and in keeping with New York State and US Federal regulations, the IRB waived the need for individual patient consent. All types of cardiac surgical procedure were eligible for inclusion, with follow-up for all outcomes of interest by extraction of data from the medical record.

A detailed description of study methodology has previously been published together with an analysis of urinary neutrophil gelatinase-associated lipocalin (NGAL) and an early ΔS_{Cr} term ($\Delta S_{Cr\text{-initial}}$) from the same cohort.[11] Briefly, following induction of general anesthesia a sample of fresh urine was collected for baseline biomarker measurement. Subsequent urine samples were typically collected within 60 minutes of separation from cardiopulmonary bypass (CPB), again at 3 hours and finally 18-24 hours after separation from CPB. Samples were processed and stored at -80ºC prior to batch analysis. Data collection included baseline characteristics and perioperative variables potentially associated with AKI or mortality available in the medical record.

At study completion, urinary cystatin-c (CyC), kidney injury molecule-1 (KIM-1), chemokine (C-C motif) ligand 2 (CCL2) and interleukin-18 (IL-18) were each measured using commercially available ELISA research kits (R & D Diagnostics, Minneapolis, MN and eBioscience, San Diego, CA). Urinary creatinine was measured by enzymatic endpoint assay (Fisher Diagnostics, Middletown, VA). Investigators conducting laboratory analyses were not formally blinded to patient outcome. Samples with undetectable biomarker levels were assigned a non-zero value placing them within the lowest quartile. S_{Cr} was measured preoperatively and then typically daily for 4 days postoperatively according to clinician judgment. The most recent S_{Cr} recorded prior to 7 am on the morning of surgery was considered baseline. All aspects of clinical care were at the discretion of the treating physician, blinded to novel urinary biomarker levels.

We hypothesized that perioperative novel urinary biomarkers would identify patients at increased risk for serious adverse outcomes reflecting AKI. The primary outcome was the composite of hospital mortality or initiation of renal replacement therapy (RRT) during the postoperative inpatient period. Secondary outcomes included individual components of the primary outcome as well as AKI defined according to Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines for AKI over 7 days postoperatively, omitting oliguric criteria.[12]

Statistical Analysis

Analyses were conducted using Stata 12 (Stata Corporation, College Station, Tx) and R version 3.1.1 (R Foundation for Statistical Computing) without imputation of missing data. We previously defined two cohort-specific creatinine-based metrics measured at time-points comparable to urinary biomarkers.[11] $\Delta S_{Cr\text{-initial}}$ was calculated as the difference in S_{Cr} from baseline to first measure after surgery while $\Delta S_{Cr\text{-peakday1}}$ was calculated as the difference in S_{Cr} from baseline to peak measure within 24 hours after surgery for use as novel thresholds against which urinary biomarkers measured within 3 hours of CPB and 18-24 hours after CPB respectively could be pragmatically compared or combined. As previously reported,[11] after adjusting for preoperative eGFR < 60 ml. $min^{-1}.1.73m^{-2}$, EuroSCORE and duration of CPB $\Delta S_{Cr\text{-initial}} \geq 0$ $mg.dL^{-1}$ was independently associated with a near 9-fold increase in odds for the primary outcome (OR 8.9, 95% CI 3.0-26.6, $p < 0.001$), similar to that observed with a KDIGO diagnosis of AKI over 7 days postoperatively (OR 9.4, 95% CI 3.0-29.5, $p < 0.001$).[a]

The study cohort was then split into quartiles for each biomarker and at each sampling time-point. The decision to use the upper quartile of the cohort to define an abnormally elevated biomarker reflects the fact that threshold values to best identify renal injury are not well established for any of the

[a]The odds ratio here differs from that in the original publication[11] reflecting subsequent exclusion from this calculation of one participant who met KDIGO AKI criteria only by commencement of RRT.

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