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Combining Functional and Tubular Damage Biomarkers Improves Diagnostic Precision for Acute Kidney Injury After Cardiac Surgery

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ABSTRACT

BACKGROUND Increases in serum creatinine (ΔSCr) from baseline signify acute kidney injury (AKI) but offer little granular information regarding its characteristics. The 10th Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) suggested that combining AKI biomarkers would provide better precision for AKI course prognostication.

OBJECTIVES This study investigated the value of combining a functional damage biomarker (plasma cystatin C [pCysC]) with a tubular damage biomarker (urine neutrophil gelatinase-associated lipocalin [uNGAL]), forming a composite biomarker for prediction of discrete characteristics of AKI.

METHODS Data from 345 children after cardiopulmonary bypass (CPB) were analyzed. Severe AKI was defined as Kidney Disease Global Outcomes Initiative stages 2 to 3 (≥100% ΔSCr) within 7 days of CPB. Persistent AKI lasted >2 days. SCr in reversible AKI returned to baseline ≤48 h after CPB. The composite of uNGAL (>200 ng/mg urine Cr = positive [+]) and pCysC (>0.8 mg/l = positive [+]), uNGAL+/pCysC+, measured 2 h after CPB initiation, was compared to ΔSCr increases of ≥50% for correlation with AKI characteristics by using predictive probabilities, likelihood ratios (LR), and area under the curve receiver operating curve (AUC-ROC) values.

RESULTS Severe AKI occurred in 18% of patients. The composite uNGAL+/pCysC+ demonstrated a greater likelihood than ΔSCr for severe AKI (+LR: 34.2 [13.0:94.0] vs. 3.8 [1.9:7.2]) and persistent AKI (+LR: 15.6 [8.8:27.5] versus 4.5 [2.3:8.8]). In AKI patients, the uNGAL−/pCysC+ composite was superior to ΔSCr for prediction of transient AKI. Biomarker composites carried greater probability for specific outcomes than ΔSCr strata.

CONCLUSIONS Composites of functional and tubular damage biomarkers are superior to ΔSCr for predicting discrete characteristics of AKI. (J Am Coll Cardiol 2014;64:2753–62) © 2014 by the American College of Cardiology Foundation.

Over the past 2 decades, the incidence of acute kidney injury (AKI) has grown exponentially and has been shown to be associated with worse outcomes in hospitalized patients (1–4). Because no singular therapy has demonstrated efficacy for mitigating the negative effects associated with AKI, mainstays of therapy include prevention and supportive care. Unfortunately, this management

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

AUC = area under the curve

CART = classification and regression tree analysis

CPB = cardiopulmonary bypass

LR = likelihood ratio

pCysC = plasma cystatin C

uNGAL = urinary neutrophil gelatinase-associated lipocalin

uNGAL+/pCysC+ = biomarker composite designating both >200 ng/mg uNGAL and >0.8 mg/l pCysC

ΔSCr = change in serum creatinine from baseline

strategy can be variable, and best practice guidelines have not yet been widely disseminated (5).

Imprecise diagnoses may lead to imprecise therapy. AKI is a syndrome caused by a wide variety of pathophysiologic processes (e.g., sepsis and post-cardiopulmonary bypass [CPB]) and does not manifest equally in all patients. Unfortunately, whereas AKI occurs along a spectrum and is heterogeneous from patient to patient, identification of AKI by serum creatinine (SCr) is binary (AKI or no AKI) and offers no ability to predict the outcome or otherwise define more specific characteristics of the injury. Additionally, the current nomenclature for AKI diagnosis is problematic. Terms such as "pre-renal" and "intrinsic renal" are simplistic and may erroneously imply specific pathophysiology, location of injury, and severity of damage, potentially leading to therapeutic imprecision. For example, fluid resuscitation, often the first course of action in a patient with severe dehydration, can be quite deleterious in a patient with congestive heart failure, even though both have the same AKI classification of "pre-renal" AKI (6). Pre-renal AKI is also often equated with a pathophysiologic description of reversibility or transient AKI, potentially rendering the erroneous conclusion that this type of AKI reflects less damage to the kidney. Intrinsic renal AKI is often considered severe and interchangeable with "acute tubular necrosis," which may be pathologically inaccurate; available histologic evidence does not consistently match the necrotic shape of renal tubules to a level of renal dysfunction (7). Thus, an approach to AKI using objective, reproducible metrics may be advantageous (8,9).

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Use of novel biomarkers indicative of different AKI pathophysiological conditions and carrying different temporal profiles in relation to injury may enhance diagnostic precision (10,11). The 10th Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) recommended testing the efficacy of novel AKI biomarkers in combination with functional biomarkers to more precisely delineate and define AKI characteristics (12). Identification of AKI phenotypes using these biomarkers may be a way to disentangle the AKI syndrome (13,14).

In this study, we tested the performance of different combinations of 2 novel biomarkers, a functional injury marker and a tubular damage marker, to refine the granularity of AKI diagnosis. We compared the abilities of these biomarker combinations to predict creatinine-based discrete AKI outcomes (using Kidney Disease Global Outcomes Initiative [KDIGO] AKI stages 2 to 3) with that of SCr itself to predict outcomes for AKI. Our findings demonstrated that combining biomarkers allows for prediction of temporal and pathophysiologic characteristics of injury, increasing the precision of AKI diagnosis in ways not possible with SCr alone.

METHODS

The Institutional Review Board of Cincinnati Children's Hospital Medical Center approved this study. The study is a retrospective review of children <18 years of age undergoing CPB, enrolled from January 2004 to May 2007 at our institution, initially in a study examining biomarkers and AKI after CPB. Before enrollment, written informed consent was obtained from the legal guardians of all patients, with assent from the patients, when appropriate (15). Patients with pre-existing kidney function insufficiency (defined as a baseline SCr concentration >2× the age-adjusted reference range) were excluded. All patients were admitted to the cardiac intensive care unit (CICU) following surgery.

Patient data were collected from the pre-operative period to CICU post-operative day 7 (POD7). Demographic data included hospital admission date, CICU admission date, CICU discharge date, hospital discharge date, prematurity; and sex, race, age, height, and weight. Procedural cardiac data collected included CPB history and CPB time; surgical complexity score using Risk Adjustment Congenital Heart Surgery Score 1 (RACHS-1) (16); and surgical procedure type. Post-operative CICU outcome data included length of stay, death, and provision of renal replacement therapy. Indices specific for kidney function included baseline SCr, first post-operative SCr, and SCr from POD1 and 2. The first post-operative SCr level was measured on arrival at the CICU, after surgery.

Data for this study included serum and urine samples. Samples were stored in aliquots at −80°C until measurement (17). Urinary biomarkers used in this study were measured 2 h after initiation of CPB, and included urinary creatinine and neutrophil gelatinase-associated lipocalin (uNGAL), measured by an enzyme-linked immunoassay kit (product no. 036, AntibodyShop, Grusbakken, Denmark) that specifically detects human NGAL (15). The concentration of serum cystatin C, also measured 2 h after initiation of CPB, was quantified by nephelometry using a standardized clinical laboratory platform (BN ProSpec, Dade-Behring, Newark, Delaware), according to the manufacturer's recommendations (18). For the original study,