Urinary Albumin Levels Predict Development of Acute Kidney Injury After Pediatric Cardiac Surgery: A Prospective Observational Study

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Objective: **Mortality and morbidity of acute kidney injury (AKI) after cardiac surgery still remain high. The authors undertook the present study to evaluate the utility of early postoperative urinary albumin (uAlb) as a diagnostic marker for predicting occurrence of AKI and its severity in pediatric patients undergoing cardiac surgery.**

Design: **A prospective observational study.**

Setting: **A single-institution university hospital.**

Participants: **All patients <18 years of age who underwent repair of congenital heart disease with cardiopulmonary bypass between July 2010 and July 2012 were included in the study. Neonates age <1 month were excluded from the study population.**

Interventions: **The association between uAlb and occurrence of AKI within 3 days after admission to the intensive care unit was investigated. Criteria from pediatric-modified Risk Injury Failure Loss and End-stage kidney disease (pRIFLE) were used to determine the occurrence of AKI. The value of uAlb was measured at intensive care unit admission immediately after cardiac surgery in all participants from whom a 5-mL urine sample was obtained.**

Measurements and Main Results: **Of 376 patients, AKI assessed by pRIFLE was identified in 243 (64.6%): 172 for risk (R; 45.7%), 44 for injury (I; 11.7%), and 27 for failure (F; 7.2%). One hundred thirty-three patients (35.4%) were classified as being without AKI (normal [N]) by pRIFLE. The concentration of uAlb was significantly higher in AKI patients than in non-AKI patients (median [interquartile range]): uAlb (μg/mL): 13.5 (6.4-39.6) *v* 6.0 (3.4-16), $p < 0.001$; uAlb/Cr (mg/gCr): 325 (138-760) *v* 121 (53-269), $p < 0.001$.**

Conclusions: **The utility of uAlb for prompt diagnosis of AKI was shown. Obtaining uAlb measurements early after pediatric cardiac surgery may be useful for predicting the occurrence and severity of AKI.**

KEY WORDS: urinary albumin, pediatric cardiac surgery, acute kidney injury

ACUTE KIDNEY INJURY (AKI) after cardiac surgery is currently the second most common cause of severe AKI in critically ill adults.[1] AKI also is an important issue after cardiac surgery in pediatric patients. Diagnosis and treatment are improving, but rates of mortality and morbidity associated with AKI after cardiac surgery in children remain high.[2–4] Early diagnosis of and intervention for AKI are particularly important for pediatric patients after cardiac surgery because pediatric cardiac patients, especially young children, may not be able to tolerate relatively small amounts of fluid overload, severe acidosis, or electrolyte disorder.

The Risk Injury Failure Loss and End-stage kidney disease (RIFLE) and the Acute Kidney Injury Network (AKIN) criteria are adult-based diagnostic tools and also are based on urine output. However, serum creatinine (sCr) concentration may not rise until 50% of kidney function has been lost. Because many studies have shown that sCr level does not parallel the patient's condition in the acute phase of AKI,[5–7] appropriate intervention or treatment might not be performed in a timely fashion.

Urinary albumin (uAlb) is one of the most important prognosis-predictive factors in chronic kidney disease.[8–10] Attention has been given recently to the importance of uAlb's role in AKI in adults.[11–13]

The aim of this study was to determine the utility of early postoperative uAlb levels in predicting the occurrence of AKI and its severity in pediatric patients who have undergone cardiac surgery.

METHODS

Study Design and Patient Population

This prospective observational study was approved by the institutional review board of Okayama University Hospital. All children <18 years of age who underwent repair of congenital heart disease under cardiopulmonary bypass (CPB), either corrective or palliative, between July 2010 and July 2012, were enrolled prospectively. All representatives of patients gave written informed consent before enrollment. Patients who underwent minor surgeries such as pacemaker implantation, release of cardiac tamponade, and diaphragmatic plication were excluded. Neonates <1 month of age also were excluded from the study population.

General Management

Anesthesia was managed mainly by administration of 20-to-50 μg/kg of fentanyl and sevoflurane. In the operating room, children with CPB received 20 mg of furosemide and 30 mg/kg of methylpredonisolone. All children received at least 50% of their

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maintenance fluid requirements during the intraoperative period and in the first 24 hours after surgery; fluids were increased in 10% increments on a daily basis if age-appropriate circulation, no lung congestion, and no tissue edema could be achieved. Patients received blood products in proportion to the amount of surgical bleeding. Target hemoglobin concentrations were 15 g/dL in children with cyanotic heart disease and 12 g/dL in children with acyanotic heart disease. During the first 24 hours, central venous pressure or left atrial pressure of 4-to-8 mmHg was the target preload. Age-appropriate blood pressure also was a goal, with dopamine, milrinone, and epinephrine used if required. If the amount of urine was <0.5 mL/kg/h for 3 hours despite adequate fluid management, use of furosemide (1 mg/kg) was considered. Criteria for performing peritoneal dialysis were urine output (UO) <0.5 mL/kg/h over a period of 4 hours despite a dose of diuretics and fluid and inotrope optimization, and serum potassium >5 mEq/L regardless of these treatments.

Urinary Albumin Measurements

A spot urine sample was taken at admission to the intensive care unit (ICU), and blood samples were taken at ICU admission and once a day during ICU stay. A 5-mL urine sample was collected immediately; 1 mL was used for measuring urinary creatinine, and the remainder of the sample was stored at –80°C for later measurement of uAlb. sCr was monitored routinely at least daily; uAlb was measured by a widely used turbidimetric immunoassay method.

Demographics and RACHS-1

The complexity of surgery was categorized according to the Risk Adjustment for Congenital Heart Surgery version 1 (RACHS-1).[14] Demographic data for patients, including age, weight, sex, CPB time, aortic cross-clamp time, complexity of surgery, duration of mechanical ventilation, and ICU length of stay, also were collected.

Definition of AKI

Pediatric-modified RIFLE (pRIFLE) criteria[15] were used to define severity of AKI. The authors determined pRIFLE by calculating estimated creatinine clearance (eCCl) using the modified Schwartz formula,[16] with "risk" defined as eCCl decrease of 25% from baseline or UO <0.5 mL/kg/h for 8 hours; "injury" defined as eCCl decrease of 50% or UO <0.5 mL/kg/h for 16 hours; and "failure" defined as eCCl decrease of 75% or absolute value of 35 mL/min/1.73 m^2, UO <0.3 mL/kg/h for 24 hours, or anuria for 12 hours on a daily basis. The latest value of sCr before surgery (usually within 7 days) was used as a baseline measurement. Severity of AKI was determined at each 3 postoperative days. Then, worst category was chosen for final categorization. Thus, loss and end-stage kidney disease were not used as part of the pRIFLE criteria in this study because diagnosis of loss and end-stage kidney disease required more than 4 weeks. Patients were divided into 3 groups by pRIFLE criteria, and the remaining patients were classified as "normal." uAlb and uAlb corrected by urinary creatinine (uAlb/Cr) were compared among the 4 groups. uAlb was corrected by urinary creatinine because the normalized concentration predicts development of AKI better.[17] Finally, patients were divided into patients in the normal category and patients with AKI (risk, injury, or failure). A receiver operating characteristic (ROC) curve was drawn to determine the performance of uAlb/Cr for prediction of the occurrence of AKI.

Statistical Analysis

JMP, version 8.1 (SAS `Institute, Cary, NC, USA), was used for statistical analysis. Data were expressed as median (interquartile range [IQR]). Continuous variables were compared using the Wilcoxon rank-sum test, and the same test was used for multiple comparisons of any pair sets. The authors compared continuous variables among groups using analysis of variance and categorical variables by using the χ^2 test, rejecting the null hypothesis at $p < 0.05$.

The performance of urinary biomarkers was determined using ROC curve analysis. Multivariate analysis for AKI also was performed to determine independent factors.

RESULTS

Clinical Information

Table 1 summarizes the patients' clinical characteristics and outcomes. A total of 376 children were included in this study. Within 3 days, AKI assessed by pRIFLE was identified in 243 patients (64.6%): 172 for risk (45.7%), 44 for injury (11.7%), and 27 for failure (7.2%). One hundred thirty-three patients (35.4%) were classified as patients without AKI (normal) by pRIFLE. Significant differences were found between the 2 groups with respect to age, body weight, surgical category, and duration of CPB.

Patients diagnosed as "higher category" in pRIFLE were much younger and smaller in weight. Longer duration of CPB resulted in a higher pRIFLE category. RACHS-1 category was lower in the normal group than in other categories. Patients with AKI had longer ICU stays (median [IQR]: 5 [3–9] *v* 3 [3–5] days, $p < 0.001$) and longer durations of mechanical ventilation (median [IQR]: 29 [7–94] *v* 6 [1–18] hours, $p < 0.001$) compared with those without AKI. Peritoneal dialysis was performed in 16 children (4.3%), and 1 death (0.3%) occurred during ICU stay. All survivors were discharged from the hospital without any kidney insufficiency.

Urinary Albumin

uAlb was measured at ICU admission after cardiac surgery. uAlb was significantly higher in AKI patients than in non-AKI patients (median [IQR], uAlb: 13.5 [6.4-39.6] *v* 6 [3.4-16] [μg/mL], $p < 0.001$; uAlb/Cr: 325 [138–760] *v* 121 [53–269] [mg/gCr], $p < 0.001$). As shown in Table 1 and Figure 1, the worse the category in pRIFLE criteria was, the higher the uAlb value, regardless of urinary creatinine correction.

Table 2 shows the results of multivariate analysis by uAlb, age, CPB time, and surgical category for AKI incidence. uAlb, age, and CPB time were independent factors for AKI incidence.

ROC Analysis of Urinary Albumin for Prediction of AKI

Figure 2 shows the results of the ROC analysis of uAlb/Cr (area under the curve 0.71; $p < 0.0001$) for