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Original Articles

Urinary albumin levels predict development of acute kidney injury following pediatric cardiac surgery: a prospective observational study

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*Structured Abstract/Summary

Abstract

Objective:

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

Design:

A prospective observational study.

Setting:

University hospital, single institution.

Participants:

All patients under 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 younger than 1 month of age were excluded from the study population.

Interventions:

The association between uAlb and occurrence of AKI within 3 days after ICU admission was investigated. Pediatric-modified RIFLE (pRIFLE) criteria were used to determine the occurrence of AKI. The value of uAlb was measured at ICU admission immediately after cardiac surgery in all participants in whom a 5-mL urine sample was obtained.

Measurements and Main Results:

Of 376 children, AKI assessed by pRIFLE was identified in 243 patients (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 patients without AKI [Normal (N)] by pRIFLE. The concentration of uAlb was significantly higher in AKI patients than in non-AKI patients [median (interquartile range; IQR)], [uAlb (µg/ml): 13.5 (6.4-39.6) vs 6.0 (3.4-16), p<0.001, urinary albumin/creatinine (uAlb/Cr) (mg/gCr): 325 (138-760) vs 121 (53-269) p<0.001].

Conclusions:

The utility of uAlb for prompt diagnosis of AKI was shown. uAlb 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,

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Acute kidney injury (AKI) after cardiac surgery is now the second most common cause of severe AKI in critically ill adult patients [1]. AKI is also 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 and early 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 a relatively small amount of fluid overload, severe acidosis, or electrolyte disorder.

RIFLE (Risk Injury Failure Loss and End-stage kidney disease) criteria and AKIN (Acute Kidney Injury Network) criteria are adult-based diagnostic tools and are also based on urine output. Serum creatinine (sCr) concentration may not rise until 50% of kidney function has been lost. Since many studies have shown that sCr level does not follow 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 recently been given to the importance of uAlb with regard to its role in AKI in adults [11-13].

The aim of this study was to determine the utility of early postoperative uAlb for predicting the occurrence of AKI and severity of illness 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 younger than 18 years of age who underwent repair of congenital heart disease under CPB, either corrective or palliative, between July 2010 and July 2012 were prospectively enrolled. 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 younger than 1 month of age were also excluded from the study population.

General Managements

Anesthesia was managed mainly by 20-50 μg/kg of fentanyl and sevoflurane. In the operating room, children with cardiopulmonary bypass received 20 mg furosemide and 30 mg/kg methylpredonisolone. All children received at least 50% of their maintenance fluid requirements during the intraoperative period and the first 24 hours after surgery with 10% increment of fluid on a daily basis if age appropriate circulation, no lung congestion, and no tissue edema could be achieved. They 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 hrs, central venous pressure or left atrial pressure of 4-8 mmHg was aimed for as a target preload. Age appropriate blood pressure were also aimed for with the use of dopamine, milrinone, and epinephrine if required. If the amount of urine was below 0.5 ml/kg/hr for 3 hours despite adequate fluid management, use of furosemide (1 mg/kg) was considered. Criteria for performing peritoneal dialysis (PD) were (1) urine output below 0.5 ml/kg/h over a period of 4 hours despite a dose of diuretics and fluid and inotrope optimization and (2) serum potassium above 5.0 mEq/L regardless of those treatments.

Urinary Albumin Measurements

A spot urine sample was taken at ICU admission and blood samples were taken at ICU admission and once a day during the ICU stay. A 5-ml urine sample was immediately collected and then 1 mL was used for measuring urinary creatinine and the remainder of the sample was stored at -80 degrees for later measurement of uAlb. sCr was routinely monitored at least daily. uAlb was measured by a widely used turbidimetric immunoassay method.

Demographics and RACHS-1

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, body weight, gender, cardiopulmonary bypass time, aortic cross clamp time, complexity of surgery, duration of mechanical ventilation and ICU stay, were also collected.

Definition of AKI

Pediatric-modified RIFLE (pRIFLE) criteria [15] were used to define severity of acute kidney injury. We determined pRIFLE by calculation of estimated creatinine clearance (eCCl) using the modified Schwartz formula [16] with "Risk" defined as eCCl decrease of 25% from baseline or urine output (UO) below 0.5 ml/kg/hr for 8 hours, "Injury" defined as eCCl decrease of 50% or UO below 0.5 ml/kg/hr for 16 hours and "Failure" defined as eCCl decrease of 75% or absolute value of 35 ml/min/1.73 m^2 or UO below 0.3 ml/kg/hr for 24 hours or anuric for 12 hours on a daily basis. The latest value of sCr before surgery (usually within 7 days) was used for baseline measurement. The worst category was chosen for severity of AKI by pRIFLE within 3 postoperative days. 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 requires more than 4 weeks. Then patients were divided into three groups by pRIFLE criteria as judged above and the remaining patients were classified as "Normal". uAlb and uAlb corrected by urinary creatinine (uAlb/Cr) were compared between the four groups. uAlb was corrected by urinary creatinine because the normalized concentration predicts development of AKI better[17]. Finally, patients were divided into patients with normal category and into patients with AKI (Risk, Injury, or Failure). A receiver operating characteristic 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, North Carolina) was used for statistical analysis. Data were expressed as medians [interquartile range (IQR)]. Continuous variables were compared using the Wilcoxon rank-sum test, and the same test was used for multiple comparison of any pair sets. We compared continuous variables between groups by using analysis of variance and compared categorical variables by using the chi-square test, rejecting the null hypothesis at $P<0.05$.

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

Role of the Funding Source

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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 two groups with respect to age, body weight, operation category, and duration of cardiopulmonary bypass.

Patients diagnosed as "higher category" in pRIFLE were much younger and smaller in weight. The longer the duration of cardiopulmonary bypass was, the higher was the pRIFLE category. RACHS-1 category was lower in Normal than in other categories. The children who experienced AKI had longer stays in the ICU [median (IQR): 5 (3-9) vs 3 (3-5) days, $p<0.001$] and longer durations of mechanical ventilation [median (IQR): 29 (7-94) vs 6 (1-18) hours, p<0.001] than did those without AKI. PD was performed in 16 children (4.3%), and one death (0.3%) occurred during the 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) vs 6.0 (3.4-16) (μg/ml); p<0.001, uAlb/Cr: 325 (138-760) vs 121 (53-269) (mg/gCr); p<0.001]. As shown in the table and figure, the worse the category in pRIFLE criteria was, the higher was uAlb regardless of urinary creatinine correction (Table 1, Fig. 1A,B).

Table 2 shows the results of multivariate analysis by uAlb, age, CPB time and operation 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 ROC analysis of uAlb/Cr (AUC 0.71; $p<0.0001$) for prediction of AKI. The optimal cutoff value for uAlb and its sensitivity, specificity, and positive and negative predictive values are shown (uAlb, cutoff 5.1, 81.9%, 46.7%, 74.1%, 58.2%: uAlb/Cr, cutoff 282, 56.0%, 77.0%, 81.9%, 48.4%).

DISCUSSION

Key Results

In a prospective cohort recruited study, we showed that uAlb at ICU admission predicts acute kidney injury after cardiac surgery in children and increases step by step according to the category of pRIFLE criteria.

Relation to Previous Studies

In a review article [18] by Pedersen, it was shown that the incidence of AKI after cardiac surgery in children varied from 2% to 42%. The reason for the variation in incidence is that the criteria used to define AKI in those studies varied from need for dialysis to elevation of serum creatinine. By using the pRIFLE criteria, the incidence of AKI after cardiac surgery in children is 36 - 67% [2-4, 19, 20]. Similarly, the incidence of AKI defined by pRIFLE criteria in the current study was 64.6%. In this study, the more severe AKI defined by pRIFLE criteria was, the higher was the rate of morbidity. This is in agreement with previous reports [3, 4].

Urinary albumin excretion may predict the development of multiorgan failure [21] and the severity of AKI in critically ill patients [13, 22]. Adult patients with severe albuminuria after cardiac surgery may be at increased risk for AKI during their hospital stay[23]. Moreover, albuminuria is associated with AKI, and its adjusted relative risk is 2.97 [24].

The results of our study support results of previous works showing the importance of albuminuria in children undergoing cardiopulmonary bypass surgery and how it relates to the development of AKI in children. Unlike other studies, our spot urine samples were taken at the time of ICU admission, whereas samples in other studies were taken 4, 6, and 24 hours after surgery [12, 25, 26]. Furthermore, we uniquely showed a step-by-step increase in urinary albumin excretion with higher categories in pRIFLE. uAlb was corrected by urinary creatinine in this study. In chronic kidney disease, uAlb corrected by urinary creatinine reduces variability of measured values due to hydration, diuretics, osmotic diuresis, and concentrating defects, and thus correction of uAlb by urinary creatinine is accepted[27]. Many

AKI biomarker studies have used normalized concentration by urinary creatinine[11, 23, 25].

Urine albumin has three potential reasons for detecting AKI. First, both ischemic AKI and toxic AKI can change a glomerular structure, and albumin filtration can therefore increase[28, 29]. Second, proximal tubular injury almost certainly disturbs albumin reabsorption as do low-molecular weight serum proteins such as B2-microglobulin and cystatin C[30]. Third, the albumin gene, which is normally silent within the kidney, is induced by AKI, as NGAL (neutrophil gelatinase-associated lipocalin) and KIM-1 (kidney injury molecule-1)[11].

Strengths and Limitations

Our study has several strengths. First, we prospectively recruited a cohort of children undergoing cardiac surgery. Second, measurement of uAlb is noninvasive. Furthermore, uAlb can be measured in almost all general hospitals throughout the world.

This study also has several limitations. The definition of AKI was based on increase in serum creatinine level, which is an unreliable measure in an acute setting. However, pRIFLE criteria have been used as a diagnostic tool for AKI in pediatric cardiac patients and critically ill children in several studies [3, 15]. Although baseline kidney function in participants was defined by serum Cr along with estimated CCl, uAlb excretion of each participant at baseline was unknown. Furthermore, the day of baseline creatinine (pre-operation) was not decided, and thus the timing of baseline creatinine measurement varied among patients.

There is a difference in the amount of uAlb depending on age, even in healthy children. By a comparison of healthy infants with adolescents, it was shown that uAlb corrected by urinary creatinine in infants is three-times higher than that in adolescents, though raw data for uAlb were not shown [31]. In a large cohort study in a European country, it was shown that there was no difference in the concentration of uAlb among all age groups but that uAlb corrected by creatinine was higher in the younger age group [32]. Although the ages of patients varied from 1 month to 18 years in our study, multivariate analysis showed the usefulness of uAlb.

Although patients with AKI were in a more severe category in RACHS-1 and received a longer duration of cardiopulmonary bypass, multivariate analysis showed that uAlb is still an independent factor. As we only showed short-term results for morbidity such as duration of ventilation and duration of ICU stay, long-term results (i.e., 6 months or 1 year status) were unknown. This may be insufficient for outcome measurement. However, none of the survivors suffered from kidney injury at hospital discharge.

Furthermore, this study was conducted at a single institution, and data analysis was not blinded. We did not show detailed hemodynamic profiles for each patient. However, attending physicians aimed at the same target for atrial pressure and age appropriate blood pressure or heart rate.

Although we showed a step-by-step increase in urinary albumin excretion with higher categories in pRIFLE, there was large inter-patient variation in uAlb. This was also a limitation.

Future Studies

Our findings indicate the need to investigate the role and source of uAlb in the pathophysiology of AKI after pediatric cardiac surgery. Kidney function in children differs depending on age. Investigation according to age in a large number of patients is needed.

In conclusion, we showed the utility of uAlb for early detection of AKI in pediatric patients who have undergone cardiac surgery. The level of uAlb early after pediatric cardiac surgery may be useful for predicting AKI in children. Validation of the utility of uAlb in a study with similar age groups is needed.

FIGURE LEGENDS

Figure 1

Comparison of urinary albumin expression for each pRIFLE category.

1A: plain urinary albumin.

1B: urinary albumin corrected by urinary creatinine.

Both graphs show a step-by-step increase in urinary albumin by pRIFLE criteria.

pRIFLE: pediatric RIFLE, N: Normal category in pRIFLE criteria, R: Risk category in pRIFLE criteria, I: Injury category in pRIFLE criteria, F: Failure category in pRIFLE criteria, uAlb: urinary albumin at ICU admission

Figure 2

ROC curves for AKI by uAlb/Cr.

AUC, cutoff value, sensitivity, specificity, PPV and NPV were 0.71, 282, 56.0%, 77.0%, 81.9% and 48.4%, respectively.

ROC: receiver operating characteristic, AUC: area under the curve, sCr:

serum creatinine, uAlb: urinary albumin at ICU admission, PPV: positive predictive value, NPV: negative predictive value

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Table 1 Patients Demographics

	N (n=133)	*R (n=172)*	*I (n=44)*	*F (n=27)*	*p*
Age (months)	32 (8-78)	17 (7-43) *	11.5 (5-37) *	8 (1-16) *†	0.0002
BW (kg)	11.4 (7-19)	8.4 (6-13) *	7.7 (5-12) *	4.7 (3-9) *†	0.0004
gender(F/M)	49/84	85/87	17/27	7/20	0.036
RACHS	2 (2-3)	2 (2-3)*	3 (3-3)* †	3 (3-3)*†	<0.0001
1	16(12.0%)	11(6.4%)	0(0%)	0(0%)	
2	78(58.6%)	78(45.3%)	10(22.7%)	5(18.5%)	
3	34(25.6%)	63(36.6%)	27(61.4%)	19(70.4%)	
4	2(1.5%)	11(6.4%)	3(6.8%)	2(7.4%)	
6	2(1.5%)	9(5.2%)	4(9.1%)	1(3.7%)	
CPB time (min)	73 (50-96)	88 (63-128) *	119 (84-178)*†	128 (89-159)*†	<0.0001
PD	0/133	2/172	3/44	11/27	<0.0001

Duration of MV (h)	6 (1-18)	20 (5-64)	51 (12-115)	70 (39-238)*†	0.018
ICU stay (days)	3 (3-5)	5 (3-7)*	8 (5-10)*†	10 (6-22)*†§	<0.0001
uAlb (µg/ml)	6.0 (3.4-16)	11.5 (5.3-31)*	28.3 (9-65)*†	38.0 (11-83)*†	0.0005
uAlb/Cr (mg/gCr)	121 (53-269)	284 (118-619)*	428 (209-1155)*†	757 (223-2025)*†	0.001
AKI incidence day					
day 1	0	76/172 (44%)	8/44 (18%)	2/27 (7%)	
day 2	0	86/172 (50%)	27/44 (61%)	12/27 (44%)	
day 3	0	10/172 (6%)	9/44 (20%)	13/27 (48%)	

N: Normal, R: Risk, I: Injury, F: Failure, BW: body weight, RACHS-1: Risk Adjustment for Congenital Heart Surgery, CPB: cardiopulmonary bypass, PD: peritoneal dialysis, MV: mechanical ventilation, ICU: intensive care unit,

uAlb: urinary albumin, Cr: creatinine

*P<0.05 vs N, †P<0.05 vs R §P<0.05 vs I

Table2

Table 2. Multivariate analysis for incidence of AKI

Item	Coefficient	Std error	P value
uAlb	0.00798832	0.0038188	0.0365*
Age	-0.0069088	0.0031326	0.0274*
CPB time	0.01224528	0.0035295	0.0005*
RACHS-1 category	0.29528138	0.1705908	0.0835

RACHS-1: Risk Adjustment for Congenital Heart Surgery, CPB: cardiopulmonary bypass, uAlb: urinary albumin, *statistically significant

Figure1A
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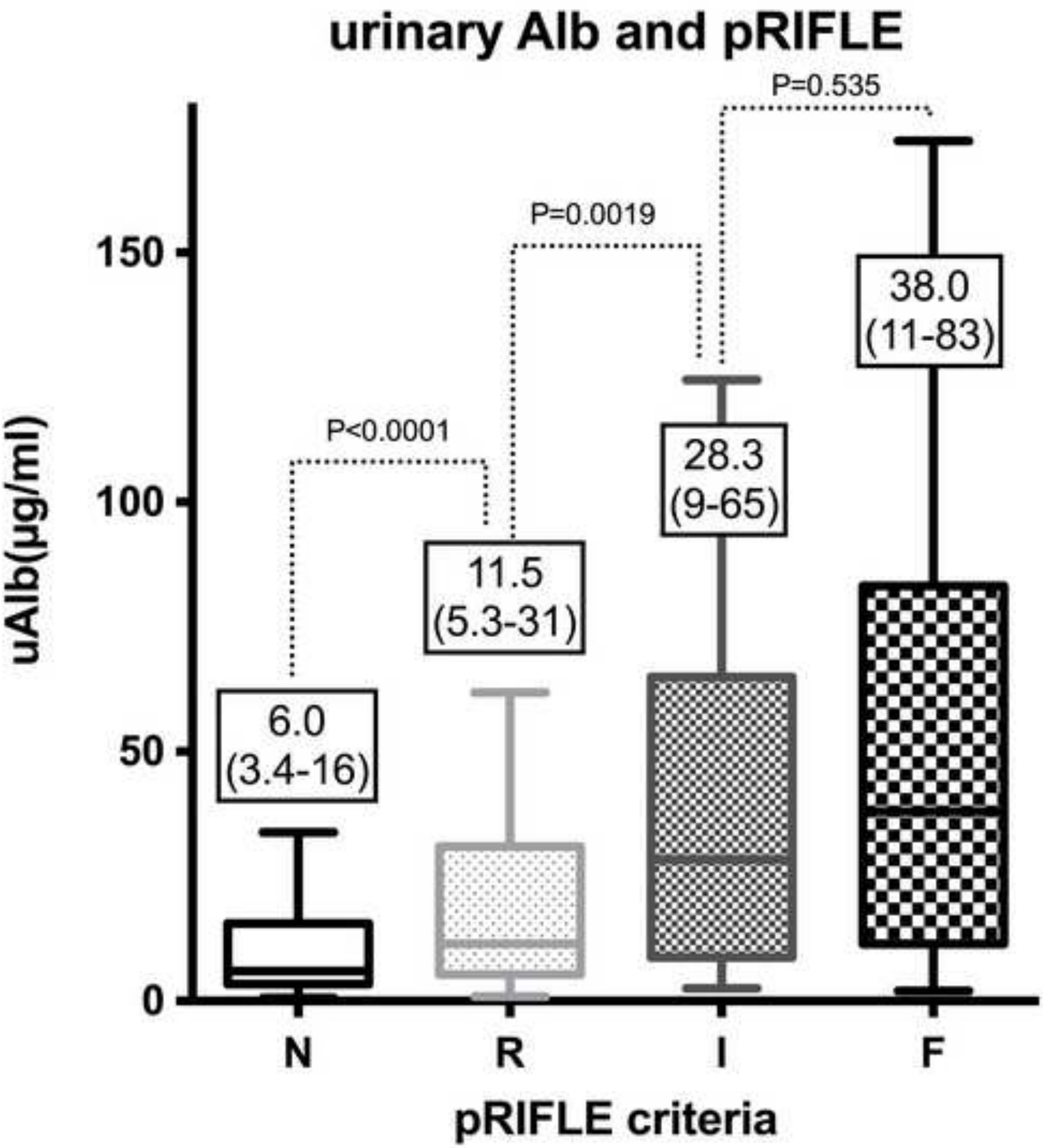

Figure1B

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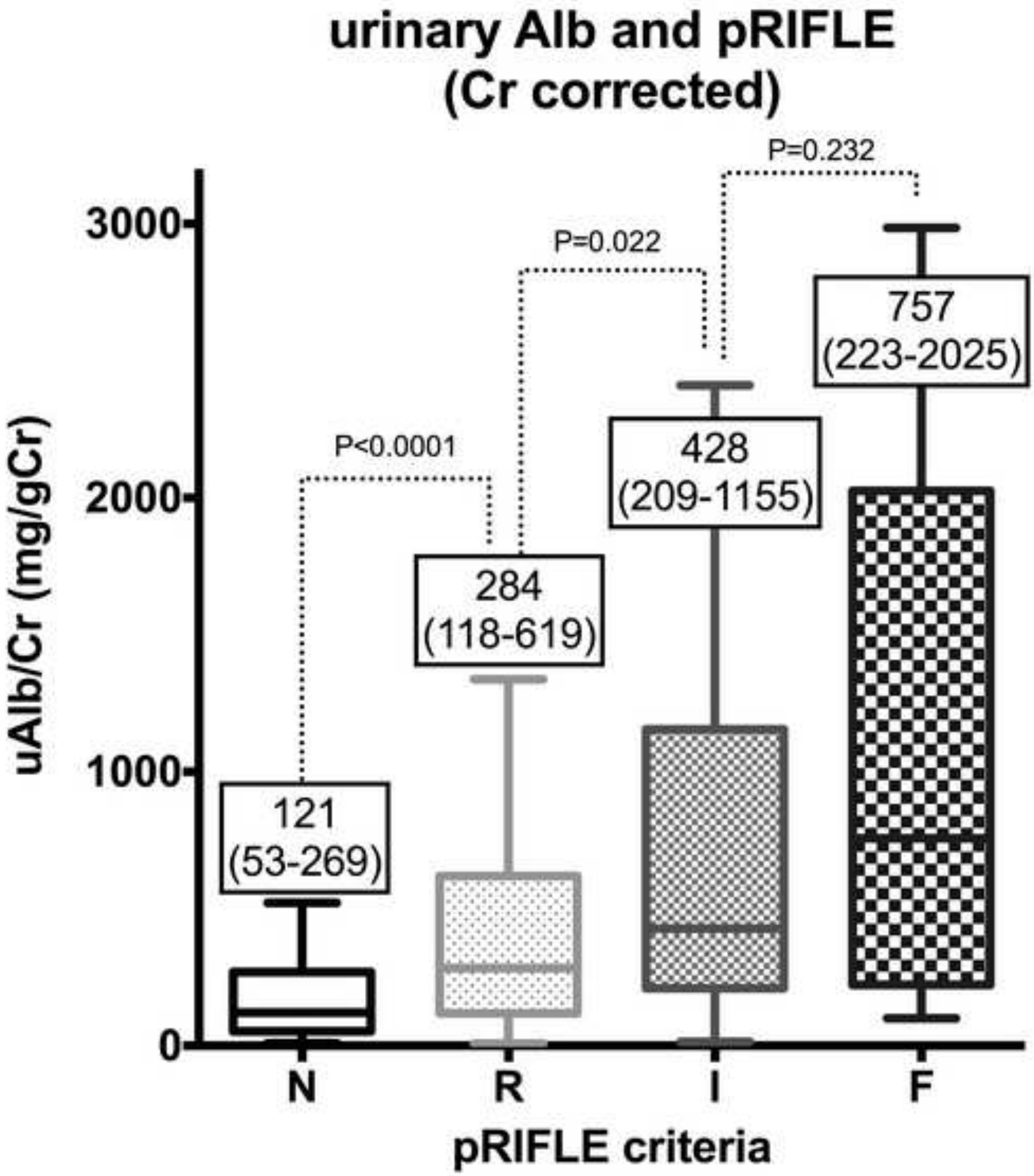

Figure2

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