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original article

Neutrophil gelatinase-associated lipocalin as an early indicator of acute kidney injury following pediatric cardiac surgery

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Abstract

Early intervention can significantly improve patient outcomes in acute kidney injury (AKI). In children with underdeveloped kidneys, it takes longer than 24 hours for serum creatinine (sCr) to peak after AKI onset. Furthermore, even very subtle increases in sCr are associated with poor outcomes, making it more difficult to diagnose early AKI in pediatric cases.

The urinary neutrophil gelatinase-associated lipocalin (NGAL) levels of 64 patients undergoing pediatric cardiac surgery using cardiopulmonary bypass from June 2018 to February 2019 were measured to evaluate NGAL as an accurate indicator of postoperative AKI.

Sixteen patients (25%) developed AKI. The AKI group showed significantly higher Risk Adjustment in Congenital Heart Surgery (RACHS-1) scores ($p=0.028$) and a significantly longer operative time ($p=0.048$), cardiopulmonary bypass time ($p=0.048$), and ventilator use time ($p<0.001$) than the non-AKI group. After surgery, urinary NGAL was significantly higher in the AKI group with a median of 37.1ng/mL (11.1-148.3) against 5.6ng/mL (1.0-35.8) of the non-AKI group ($p=0.021$). Using a cut-off value of 11.9ng/mL, the area under the curve of urinary NGAL for predicting AKI was 0.69, the sensitivity was 75%, and the specificity was 44%.

Higher RACHS-1 scores are associated with postoperative AKI. Urinary NGAL shows a moderate correlation with AKI diagnosis, and may be useful for predicting AKI early in the perioperative period.

Key words: neutrophil gelatinase-associated lipocalin (NGAL), acute kidney injury (AKI), pediatric cardiac surgery, cardiopulmonary bypass, The Risk Adjustment in Congenital Heart Surgery (RACHS-1) system

Ⅰ. Introduction

Risk factors for postoperative acute kidney injury (AKI) in patients undergoing cardiac surgery include ischemic-reperfusion injury associated with microcirculatory dysfunction due to non-physiological hemodynamics from cardiopulmonary bypass (CPB) and inflammatory reaction due to the exposure of blood to the CPB circuit [1)]. The incidence of AKI after CPB is reported to be as high as 20-30% [2)]. AKI severity has a linear relationship with mortality [3)], but it has been shown that even a 0.3mg/dL increase in serum creatinine (sCr) can affect prognosis and treatment course [4)]. This highlights the importance of early AKI diagnosis for improving patient outcomes through early initiation of therapeutic interventions.

In 2011, to facilitate early detection of AKI, Kid-

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ney Disease:Improving Global Outcomes (KDIGO) defined the diagnostic criteria for AKI as the presence of oliguria for 6 hours and an increase in sCr within 48 hours [5]. Although the use of the KDIGO criteria has been validated in pediatric cases [6], the reference values of sCr for pediatric patients are highly variable. In newborns, as a result of the maternal transfer of creatinine, sCr levels can vary day by day [7], and in early childhood, sCr increases with age [8]. Furthermore, in children, sCr can take longer than 24 hours to peak after AKI onset [9], and even a small rise in sCr is shown to be associated with poor clinical outcomes [10]. Since the rise in sCr is too small to make a determination, in patients under the age of 18, AKI can be diagnosed using estimated glomerular filtration rate (eGFR) [5]. However, AKI diagnosis using eGFR may not be suitable in neonates whose renal function is not yet mature [6]. Furthermore, a common eGFR equation may not be accurate due to differences in body composition between Caucasian and Japanese children [11]. Given these limitations, a more sensitive marker of early AKI in pediatric cases is thus required.

Neutrophil gelatinase-associated lipocalin (NGAL) is rapidly expressed by renal epithelial cells following AKI and accumulates in the urine due to reduced reabsorption in the proximal tubule [12, 13]. Recent studies have reported the usefulness of NGAL in the early diagnosis of AKI [14-18]. Indeed, in the 2016 Japanese Clinical Practice Guideline for Acute Kidney Injury, NGAL was given the highest class of recommendation and level of evidence among urinary biomarkers [19].

This aim of this study was to evaluate the effectiveness of urinary NGAL as an early indicator of AKI in patients undergoing pediatric cardiac surgery using CPB.

Ⅱ. Method

1. Population

This study included 67 consecutive patients who underwent pediatric cardiac surgery with CPB from June 2018 to February 2019 in our institution. Patients were stratified into AKI and non-AKI groups using the KDIGO criteria [5], as recommended by the 2016 Japanese Clinical Practice Guideline for Acute Kidney Injury [19].

2. Urinary NGAL evaluation

Written informed consent was obtained from the parents of each patient, and the study was approved by the Institutional Review Board of Juntendo University Hospital (approval number 17-304). Urine collection was performed a total of nine times - before and 0, 1, 2, 4, 8, 12, 24, and 72 hours after admission to the intensive care unit. Each sample was centrifuged at a relative centrifugal force of 500G for 5 minutes and then stored at -80oC. Urinary NGAL was measured by a chemiluminescence immunoassay using an ARCHITECT i200SR® immunoassay analyzer (Abbott Japan Co., Ltd,Tokyo,Japan). Absolute urinary NGAL values, not creatinine-adjusted NGAL concentrations, were used to evaluate the role of urinary NGAL in the early diagnosis of AKI.

3. CPB

For CPB, the priming volume was calculated according to institutional protocol with the target flow rate based on a perfusion index (PI) of 2.6L/min/m^2. Body temperature was maintained at mild to moderate hypothermic levels. Blood transfusion was used to correct low hematocrit values (lower limit of 18%) whenever feasible. In all cases, modified ultrafiltration was performed immediately after CPB discontinuation.

4. Perioperative management

Perioperative management was performed by an anesthesiologist and by a cardiovascular surgeon after surgery. Hemodynamic management involved the administration of dopamine, dobutamine, noradrenaline, and nitroglycerin as appropriate. Ventilation management was mainly performed via pressure control ventilation, and nitric oxide (NO) therapy was used in cases of poor oxygenation or high pulmonary arterial pressure.

5. Data collection

Demographic and clinical data collected included patient background, operative time, CPB time, aortic cross-clamp time, postoperative ventilation use time, pre- and post-operative PaO_2/FiO_2 (P/F) ratio, and NO therapy use. Intraoperatively, mean arterial blood pressure (mBP), PI, cerebral regional oxygen saturation (rSO_2), and abdominal rSO_2. were recorded every 10 minutes. Hemoglobin (Hgb) and hematocrit (Hct) were measured every 20 minutes and used to calculate oxygen supply (DO_2), carbon dioxide emissions (VCO_2), and DO_2/VCO_2 ratio. In addition, pre-

and postoperative serum lactic acid levels and platelet levels were compared. sCr was evaluated before and 12 and 36 hours after the operation.

The Risk Adjustment in Congenital Heart Surgery (RACHS-1) system devised by Jenkins et al [20]. was used to classify the cases according to surgical outcome.

6. Statistical analysis

Nonparametric tests and logistic regression analysis were performed using JMP® 13.2 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered statistically significant. The diagnostic value of NGAL was determined using receiver operating characteristic (ROC) curve analysis. The optimal cut-off value for AKI diagnosis was defined as the point on the ROC curve which maximized the Youden index (sensitivity+specificity−1).

Ⅲ. Results

A total of 67 cases were included in this study. Three cases were excluded due to missing data. Of the 64 patients, 16 (25%) developed AKI according to the KDIGO criteria. Of these 16 patients, 10 (16%) had stage 1, 4 (2%) had stage 2, and 2 (3%) had stage 3 AKI (**Table 1**). There were no cases of congenital kidney disease, blood purification therapy such as peritoneal dialysis, or postoperative death in the AKI or non-AKI group.

Table 1 Classification of the acute kidney injury diagnosis group according to disease stage using KDIGO guidelines

	n=64 (AKI groups n=16；25%)
AKI Stage1	n=10；16%
AKI Stage2	n=4；6%
AKI Stage3	n=2；3%

AKI：acute kidney injury.

The median RACHS-1 score of the AKI group was higher than that of the non-AKI group (3.0 vs 2.0；p=0.028). The median operative time (232 vs 184 minutes；p=0.048) and median CPB time (97.5 vs 66.5 minutes；p=0.048) of the AKI group were longer than those of the non-AKI group.

With regards to intraoperative CPB parameters, the AKI group exhibited a lower median abdominal rSO_2 (72% vs 75%) and a higher rSO_2 reduction rate (7.4% vs 2.1%) then the non-AKI group. Both differences were statistically significant ($p<0.001$).

Median serum lactic acid levels after CPB were higher in the AKI group (1.4 vs 1.1；p=0.044). The AKI group also exhibited significantly higher sCr values 12 hours after surgery (median：0.57 vs 0.36；$p<0.001$). Notably, two patients in the AKI group exhibited a maintained increase in sCr even after 36 hours.

Longer ventilation use was observed in the AKI group (48 vs 2 hours；p=0.037). There was one tracheostomy case in the AKI group (6.3%) and five in the non-AKI group (10.4%). NO therapy was used in five cases in the AKI group (31.3%) and ten cases in the non-AKI group (20.8%) (**Table 2.3.4**).

Table 2 Patient characteristics and clinical outcomes

	non-AKI group (n=48)	AKI group (n=16)	*p*-value
Age (months)	32.5 (10.0-67.8)	11.0 (6.8-22.5)	0.066 (NS)
Weight (kg)	11.6 (6.8-17.9)	7.7 (6.0-11)	0.546 (NS)
BSA (m^2)	0.52 (0.40-0.72)	0.41 (0.29-0.52)	0.297 (NS)
RACHS-1 score	2.0 (2.0-3.0)	3.0 (2.0-3.0)	0.028 *
OP time (min)	184.0 (150.5-238.8)	232.0 (163.0-307.5)	0.048
CPB time (min)	66.5 (51.8-107.5)	97.5 (67.3-138.8)	0.048
Cardiac arrest time (min)	38.0 (19.8-107.5)	39.0 (21.0-99.5)	0.376 (NS)
Post OP intubation time (min)	2.0 (0.0-41.3)	48.0 (16.5-80.5)	<0.001
Pre OP P/F ratio (mmHg)	301.9 (155.0-474.4)	217.0 (99.6-342.3)	0.145 (NS)
Post OP P/F ratio (mmHg)	462.0 (314.3-528.5)	432.0 (185.3-468.5)	0.104 (NS)
Inhaled nitric oxide therapy (n (%))	10 (20.8%)	5 (31.3%)	0.330 (NS)
Pre OP serum lactate (mmol/L)	0.8 (0.7-1.1)	1.0 (0.8-1.1)	0.844 (NS)
Post OP serum lactate (mmol/L)	1.1 (0.9-1.4)	1.4 (1.2-1.9)	0.044
Pre OP sCr (mg/dL)	0.32 (0.24-0.38)	0.26 (0.21-0.34)	0.43 (NS)
Post OP 12 h sCr (mg/dL)	0.36 (0.28-0.48)	0.57 (0.43-0.62)	<0.001
Post OP 36 h sCr (mg/dL)	0.30 (0.22-0.38)	0.31 (0.27-0.35)	0.25 (NS)

Data are presented as median (interquartile range).
AKI：acute kidney injury, BSA：body surface area, RACHS-1：risk adjustment in congenital heart surgery system, OP：operative, CPB：cardiopulmonary bypass, P/F：PaO_2/FiO_2, sCr：serum creatinine, h：hours.
* $p<0.05$ in the legend

Table 3 Surgical procedures categorized by RACHS-1 score

	non-AKI group (n=48)	AKI group (n=16)
Category 1		
ASD closure	10	2
Category 2		
VSD closure	16	3
Coarctation repair	2	0
Tetralogy of Fallot repair	1	1
Bidirectional Glenn shunt	1	0
Category 3		
DORV repair	6	1
Fontan procedure	4	2
Fontan+ Fenestrated	0	1
Arterial switch operation	3	1
Coarctation repair+PA banding	1	0
Complete AVSD repair	0	1
Glenn+PA banding	1	0
Central shunt	1	0
VSD closure+tricuspid valvuloplasty	1	0
Tricuspid valvuloplasty	0	1
Pulmon aryatresia+VSD closure	0	1
Cor triatriatum repair	1	0
Category 4		
Rastelli procedure	0	1
TAPVC repair	0	1

AKI : acute kidney injury, ASD : atrial septal defect, VSD : ventricular septal defect, DORV : double outlet right ventricle, PA : pulmonary artery, AVAD : atrioventricular septal defect, TAPVC : total anomalous pulmonary venous connection
No patients underwent category 5 or 6 procedures.

Table 4 Cardiopulmonary bypass clinical outcomes

	non-AKI group (n=48)	AKI group (n=16)	*p*-value
mBP (mmHg)	38.0 (32.0-45.0)	36.0 (31.0-40.0)	0.134 (NS)
PI (L/min/m^2)	2.4 (2.2-2.7)	2.4 (2.2-2.6)	0.478 (NS)
HGB (g/dL)	8.6 (7.8-9.9)	8.9 (7.7-10.7)	0.067 (NS)
HCT (%)	26.0 (23.1-29.8)	27.0 (23.0-31.0)	0.090 (NS)
Cerebral rSO_2 (%)	69.0 (61.0-76.0)	71.0 (63.0-78.0)	0.074 (NS)
Cerebral rSO_2 deterioration rate (%)	15.2 (9.7-23.7)	11.0 (3.2-22.7)	0.43 (NS)
Abdominal rSO_2 (%)	75.0 (47.8-83.0)	72.0 (62.0-81.0)	<0.001
Abdominal rSO_2 deterioration rate (%)	2.1 (0.0-6.2)	7.4 (4.0-17.8)	0.03
DO_2 (mL/min/m^2)	280.1 (231.9-324.6)	306.4 (256.3-361.2)	0.117 (NS)
VCO_2 (mL/min)	78.9 (62.4-97.4)	77.5 (65.2-89.6)	0.844 (NS)
DO_2/VCO_2 ratio	3.7 (2.9-4.4)	4.0 (3.1-4.7)	0.70 (NS)

Data are presented as median (interquartile range).
AKI : acute kidney injury, mBP : mean blood pressure, PI : perfusion index, HGB : hemoglobin, HCT : hematocrit, rSO_2 : regional oxygen saturation, DO_2 : oxygen delivery, VCO_2 : volume of exhaled carbon dioxide

After surgery, the AKI group showed increased urinary NGAL levels (0 hour : 37.1ng/mL vs 5.6ng/mL ; p=0.021). This trend continued throughout the first 2 hours after surgery, but no significant differences were found between the two groups from 4 hours onwards (**Fig.1 ; Table 5**).

The diagnostic value of urinary NGAL was evaluated. After the operation, using a cut-off value of 11.9ng/mL, the area under the curve (AUC) was 0.69, the sensitivity was 75%, and the specificity was 44%. One hour after the operation, using a cut-off value of 7.8ng/mL, the AUC was 0.69, the sensitivity was 75%, and the specificity was 42%. Two hours after the operation, using a cut-off value of 8.1ng/mL, the AUC was 0.68, the sensitivity was 56%, and the specificity was 35% (**Fig.2 ; Table 6**).

Ⅳ. Discussion

Studies have shown a correlation between low intraoperative perirenal rSO_2 values and the development of postoperative AKI following pediatric cardiac surgery [21, 22]. In this study, although the derived val-

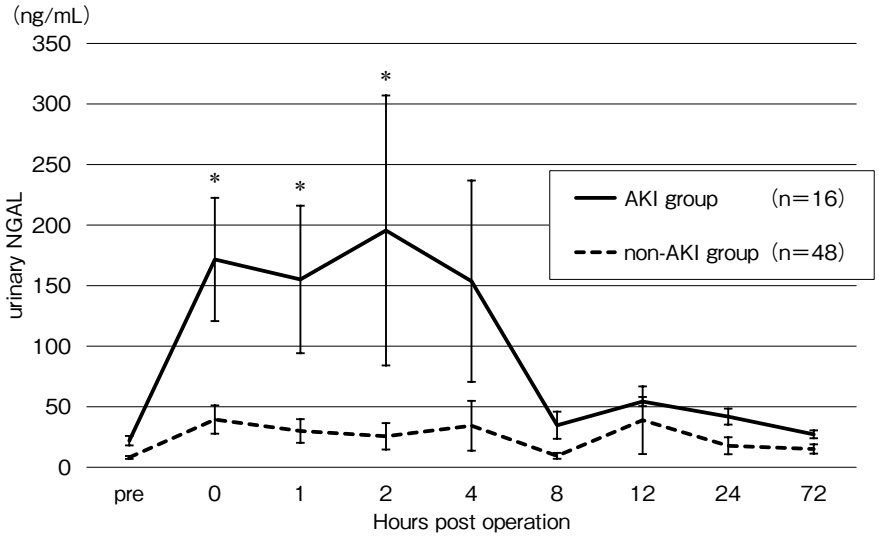

Fig.1 Analysis of urinary neutrophil gelatinase-associated lipocalin

Data are presented as mean ± SEM.

* $p < 0.05$ AKI groups vs. non-AKI groups. AKI : acute kidney injury diagnosis.

Table 5 Pre- and postoperative urinary neutrophil gelatinase-associated lipocalin levels

Time after OP (h)	non-AKI group (n = 48) * (ng/mL)	AKI group (n = 16) * (ng/mL)	non-AKI group (n = 48) ** (ng/mL)	AKI group (n = 16) ** (ng/mL)	*p*-value
pre	5.8 (1.9-12.3)	6.9 (4.6-16.3)	8.1 ± 1.2	13.8 ± 3.9	0.084 (NS)
0	5.6 (1.0-35.8)	37.1 (11.1-148.3)	39.4 ± 11.7	132.2 ± 50.9	0.021
1	3.7 (0.5-16.6)	19.9 (6.7-78.6)	30.0 ± 9.8	125.1 ± 60.9	0.030
2	2.1 (0.6-6.6)	11.4 (2.3-62.9)	25.6 ± 10.9	170.0 ± 111.5	0.045
4	2.7 (1.4-9.0)	6.6 (2.7-24.6)	34.3 ± 20.5	119.4 ± 83.1	0.210 (NS)
8	3.8 (1.8-8.5)	11.1 (4.8-20.9)	9.4 ± 2.4	25.3 ± 11.2	0.070 (NS)
12	4.2 (1.4-10.1)	8.8 (7.2-17.8)	38.9 ± 27.9	15.4 ± 3.8	0.586 (NS)
24	4.9 (1.4-10.1)	17.7 (4.9-28.7)	17.8 ± 7.0	24.1 ± 6.6	0.634 (NS)
72	6.3 (2.4-10.7)	6.4 (2.9-16.8)	15.1 ± 3.8	12.1 ± 3.2	0.659 (NS)

* Data are presented as median (interquartile range) ; ** Data are presented as mean ± SEM

AKI : acute kidney injury, OP : operative, h : hours

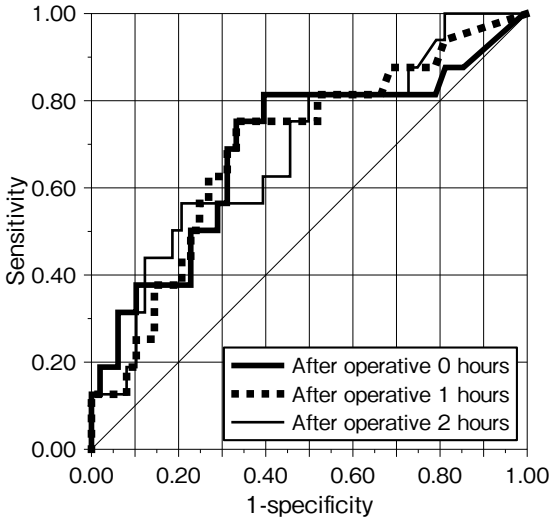

Fig.2 Receiver operating characteristic curves of urinary neutrophil gelatinase-associated lipocalin in acute kidney injury diagnosis

Table 6 Performance of urinary neutrophil gelatinase-associated lipocalin in acute kidney injury diagnosis

Time after operation (h)	AUC	Cut-off value	Sensitivity	1-specificity
pre	0.61	4.2	0.81	0.25
0	0.69	11.9	0.75	0.42
1	0.69	7.8	0.75	0.42
2	0.68	8.1	0.56	0.35
4	0.67	6.1	0.60	0.33
8	0.73	9.0	0.67	0.43
12	0.32	54.4	1.00	0.63
24	0.72	20.3	0.50	0.40
72	0.47	0.0	0.20	0.09

h : hours, AUC : area under the curve

Table 7 Comparison of studies for early diagnosis of acute kidney injury (AKI)

	Bennett M	This study
RACHS-1 score	1.6±0.5 vs 2.9±0.6	2.2±0.1 vs 2.6±0.2
urinary NGAL (ng/mL)	53.0±20.7 vs 646.3±69.8 *	39.4±11.7 vs 132.2±50.9 **

Data are presented as mean±SEM for non-AKI vs. AKI.
* First time interval that showed significant results ; ** 2 hours post-cardiopulmonary bypass
0 hours post-operative.

ues are nonspecific, the decreasing rSO_2 and increased lactic acid levels point towards hypoperfusion and metabolic issues in the abdominal region.

Twelve hours after the operation, the maximum and minimum values of sCr in the AKI group were 1.29mg/dL and 0.3mg/dL, respectively, compared to the reference values of 0.38mg/dL and 0.16mg/dL. This correlates with other studies that have reported that in pediatric cases where the baseline values of sCr are very low, even a small rise in sCr can predict AKI [8].

Several studies in both adult and pediatric cases have shown that urinary NGAL increases significantly in AKI and may be an early biomarker of AKI [14-18]. In a similar study conducted by Bennett et al [14], the AKI group had significantly higher RACHS-1 scores (2.9±0.6 vs 1.6±0.5) and higher urinary NGAL values 2 hours after CPB (646.3±69.8ng/mL vs 53.0±20.7ng/mL) than the non-AKI group. The present study also found that the AKI group exhibited significantly higher RACHS-1 scores (2.6±0.2 vs 2.2±0.1) and urinary NGAL levels after surgery (132.2±50.9ng/mL vs 39.4±11.7ng/mL) (**Table 7**) . Although the urinary NGAL values obtained were lower in the present study, results were very similar, particularly the earliest time-point at which urinary NGAL levels became significantly elevated. These results support the idea that urinary NGAL may be an early biomarker of renal failure.

Clinical investigations suggest that AKI is not only an indicator of renal failure, but is also associated with multiorgan dysfunction. One such extrarenal effect of AKI is pulmonary dysfunction, which is mediated via different mechanisms including increased lung vascular permeability and neutrophil infiltration [23, 24]. A previous study reported an association between high RACHS-1 scores and longer ventilator use [25]. In the present study, although there was no significant difference in P/F ratio among the more complicated cardiac surgical cases in the AKI group, there was a tendency towards prolonged ventilator use and NO therapy in this population, which suggests pulmonary dysfunction from the remote effects of AKI.

The importance of early diagnosis and therapeutic intervention for AKI was advocated in the Japanese Clinical Practice Guideline for AKI 2016 [19]. Monitoring changes in urinary NGAL can be useful in the early diagnosis of AKI, and can help to reduce and prevent postoperative complications. However, when compared to other urinary biomarkers, NGAL appears to be less sensitive and specific because NGAL levels are affected by systemic inflammatory reactions such as those caused by pneumonia and urinary tract infection [26]. Indeed, in this study, there was a substantial variation in the NGAL values obtained. This suggests that AKI diagnosis requires a comprehensive clinical evaluation of creatinine levels against urinary biomarkers as well as the use of multiple biomarkers and testing methods.

This suggests that AKI diagnosis may require the use of multiple biomarkers and testing methods.

Ⅴ. Conclusion

In this study, urinary NGAL was evaluated as an early indicator of AKI after pediatric cardiac surgery using CPB.

The group of patients who developed AKI showed higher RACHS-1 scores and longer operative and CPB times. While urinary NGAL in this AKI group was found to moderately predict AKI, exhibiting AUC values of 0.7 or higher during the early postoperative period, there was substantial variation in the NGAL values obtained.

Urinary NGAL has a moderate correlation with AKI occurrence, and may be useful for predicting AKI early in the perioperative period after pediatric cardiac surgery cases using CPB.

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REFERENCES

1) Parida S, Badhe AS：Cardiac surgery-associated acute kidney injury. J Anesth, 27 (3)；433-446, 2013.
2) Kumar AB, Suneja M：Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology, 114 (4)；964-970, 2011.
3) Doi K, Negishi K, Noiri E, et al.：Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. Crit Care Med, 39 (11)；2464-2469, 2011.
4) Lassnigg A, Schmidlin D, Hiesmayr M, et al.：Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery：a prospective cohort study. J Am Soc Nephrol, 15 (6)；1597-1605, 2004.
5) Kidney Disease：Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int, 2 (Suppl 1)；1-138, 2012.
6) Selewski DT, Cormell TT, Gipson DS, et al.：Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med, 40 (10)；1481-1488, 2014.
7) Guignard JP, Drukker A：Why do newborn infants have a high plasma creatinine?. Pediatrics,103 (4)；e49, 1999.
8) Uemura O, Honda M, Kitagawa T, et al.：Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children：a multicenter study. Clin Exp Nephrol, 15 (5)；694-669, 2011.
9) Mishra J, Dent C, Devarajan P, et al.：Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet, 365 (9466)；1231-1238, 2005.
10) Lassnigg A, Schmid ER, Schmidlin D, et al.：Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery：do we have to revise current definitions of acute renal failure? Crit Care Med, 36 (4)；1129-1137, 2008.
11) Uemura O, Honda M, Iijima K, et al.：Is the new Schwartz equation derived from serum creatinine and body length suitable for evaluation of renal function in Japanese children?. Eur J Pediatr, 171 (9)；1401-1404, 2012.
12) Mori K, Lee HT, Barasch J, et al.：Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest, 115 (3)；610-621, 2005.
13) Kuwabara T, Mori K, Nakao K, et al.：Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int, 75 (3)；285-294, 2009.
14) Bennett M, Dent C, Devarajan P, et al.：Urine NGAL predicts severity of acute kidney injury after cardiac surgery：a prospective study. Clin J Am Soc, Nephrol, 3 (3)；665-673, 2008.
15) Mishra J, Dent C, Devarajan P, et al.：Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet, 365 (9466)；1231-1238, 2005.
16) Zappitelli M, Washburn KK, Goldstein SL, et al.：Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children：a prospective cohort study. Crit Care, 11 (4)；R84, 2007.
17) Parikh CR, Devarajan P, Krawczeski CD, et al.：Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol. 22 (9)；1737-1747, 2011.
18) Liebetrau C, Dorr O, Weber M, et al.：Neutrophil gelatinase-associated lipocalin (NGAL) for the early detection of cardiac surgery associated acute kidney injury. Scand J Clin Lab Invest, 73 (5)；392-399, 2013.
19) Doi K, Nishida O, Terada Y, et al.：The Japanese clinical practice guideline for acute kidney injury 2016. Clin Exp Nephrol, 22 (5)；985-1045, 2018.
20) Jenkins KJ：Risk adjustment for congenital heart surgery：the RACHS-1 method. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 7；180-184, 2004.
21) Adams PS, Vargas D, Toledo J, et al.：Associations of perioperative renal oximetry via near-infrared spectroscopy, urinary biomarkers, and postoperative acute kidney injury in infants after congenital heart surgery：should creatinine continue to be the gold standard?. Pediatr Crit Care Med, 20 (1)；27-37, 2019.
22) Guinot PG, Bernard E, Dupont H, et al.：Doppler-based renal resistive index can assess progression of acute kidney injury in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth, 27 (5)；890-896, 2013.
23) Grams ME, Rabb H：The distant organ effects of acute kidney injury. Kidney Int, 81 (10)；942-948, 2012.
24) Yap SC, Lee HT：Acute kidney injury and extrarenal organ dysfunction：new concepts and experimental evidence. Anesthesiology, 116 (5)；1139-1148, 2012.
25) Taniguchi A, Hosokawa K, Shime N：Factors associated with early extubation after pediatric cardiac surgery. J Jpn Soc Intensive Care Med. 19 (2)；197-202, 2012.
26) Wagener G, Gubitosa G, Lee HT, et al.：Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis, 52 (3)；425-433, 2008.