Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/28

Original Article

Acute Kidney Injury According to Modified Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease Criteria in the Pediatric Intensive Care Unit: Risk Factors

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Abstract

Background: Acute kidney injury (AKI) classification using Pediatric Modified Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) criteria revealed that AKI is very common in critically ill pediatric patients and is associated with significant morbidity and mortality. Hence, we decided to conduct a study to determine the incidence and risk factors of AKI in pediatric intensive care unit (PICU) patient using pRIFLE criteria.

Materials and Methods: Suspected risk factors for AKI such as age <1 year, weight <10 kg, male gender, pre-existing illness, the pediatric risk of mortality score [PRISM III] (PRISM SCORE) at the day of admission, suspected or proven sepsis, multiorgan dysfunction syndrome, need for ventilator support, duration of ventilation, use of intravenous radiocontrast, use of liposomal amphotericin, use of acyclovir, use of diuretics, use of blood products, and use of noradrenalin were recorded in predesigned assessment sheet. Serum creatinine (estimated creatinine clearance) and urine output were monitored to classify patients into two groups AKI (risk, injury, and failure by modified pRIFLE criteria) and no AKI and then the suspected risk factors were analyzed using univariate and multivariate logistic regression analysis.

Results: Out of 114 patients, 50 patients developed AKI 64 patients (56.2%) did not developed AKI during the study period and served as controls; 23 patients (20.1%) developed pRIFLEmax R AKI; 15 (13.1%) pRIFLEmax I and 12 (10.5%) pRIFLEmax F AKI. Univariate analysis showed that the length of stay in PICU >4 days, PRISM III score >10 and ≥4 days on ventilator support were significant predictors of AKI ($P < 0.01$) whereas multivariate logistic regression analysis showed only the use of diuretics had a protective role in AKI (89.1% vs. 74%, $P = 0.047$, odds ratio of 0.324, and 95% confidence interval: 0.107-0.85), whereas other factors had no role in AKI.

Conclusion: Multidimensional AKI classification and stratification systems, such as pRIFLE, can serve well to improve understanding of AKI epidemiology and potentially optimize evaluation and treatment for AKI in children.

Key words: Acute kidney injury, Modified risk, injury, failure, loss, end-stage kidney disease criteria, Pediatric intensive care unit

INTRODUCTION

The reported mortality from acute kidney injury (AKI) is still as high as 60% in critically ill children.[1] Most of the reported clinical studies of pediatric AKI focus on patients requiring renal replacement therapy, who have clearly experienced severe renal injury.[1] However, recent studies demonstrate that even a modest rise in serum creatinine (SCr) is a risk factor for mortality in adult and pediatric patients.[1,2]

The AKI diagnosis criteria are defined as "an abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in SCr of more than or equal to 0.3 mg/dL, a percentage increase in SCr of more than or equal to 50% (1.5-fold from baseline), or a reduction in

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www.ijss-sn.com

Month of Submission : 11-2016
Month of Peer Review : 12-2016
Month of Acceptance : 12-2016
Month of Publishing : 01-2017

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urine output (UOP) (documented oliguria of <0.5 ml/kg/h for more than 6 h)."[3] This definition considers the patient's baseline function and changes in clinical markers within a 48-h.

In 2004, the acute dialysis quality initiative proposed a multidimensional AKI classification system in adults termed the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) criteria to promote a consistent AKI definition to compare findings across studies and populations.[4]

AKI plays a major role in the clinical outcomes of critically ill patients. It is estimated that AKI affects approximately 35% of intensive care patients and 4-7% of all hospitalized patients.[5]

Although creatinine level and UOP are not highly sensitive indicators of glomerular filtration rate, they are readily available, clinically tested and verified, and therefore used in most definitions.[6-8]

This study was performed considering the paucity of data available on the incidence and determinants of AKI in Indian children and taking into account the retrospective nature of the previous studies.

Objectives of the Study

To correlate risk factors in children who developed AKI with those who did not develop AKI.

MATERIALS AND METHODS

This was a prospective study that validated pediatric modified RIFLE (pRIFLE) criteria for defining AKI in critically ill children done over a period of 1 year at Narayana Hrudayalaya Multispeciality Hospital, Bengaluru, India. The study was approved by the Institutional Ethics Committee. Informed consent was obtained from the parents before the inclusion of subjects into the study.

Patients aged 1 month to 14 years, admitted to the pediatric intensive care unit (PICU), were eligible for enrollment. Patients with known renal disease and immediately following renal transplantation were excluded. Patients with less than two SCr levels or those with no urine specimens were also excluded from the study. Patients were enrolled within 48 h of admission in the PICU and followed for up to 10 days from enrollment or until PICU discharge.

The clinical variables collected for this study were age, gender, weight, admission and discharge diagnoses, and pre-existing illness: Present/absent, length of stay in PICU, and pediatric risk of mortality score (PRISM III score) (PRISM III, a severity of illness/mortality risk measure) were calculated at the day of PICU admission, need for mechanical ventilation, number of days on mechanical ventilation, use of noradrenalin, use of liposomal amphotericin, antiviral used (acyclovir), use of diuretics, use of intravenous (IV) radiocontrast, use of blood products, sepsis present or absent: Patients were classified as having sepsis if they fulfilled consensus criteria for systemic inflammatory response syndrome, infection, sepsis, and severe sepsis or septic shock suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) as determined from PICU admission/discharge summaries and laboratory values. Multiorgan dysfunction syndrome (MODS): Presence of >2 altered organ functions such that homeostasis cannot be maintained without medical intervention.

Classification of patients according to pRIFLE criteria (Table 1): Serum Cr values and UOP (in ml/kg/h 8th hourly) were recorded on day 1, 2, 3, 7, and possibly day 10 of PICU stay. Estimated creatinine clearance (eCCl) was calculated using the Schwartz formula (eCCl = K Ht/Sr Creatinine). Patients were classified daily by pRIFLE criteria for AKI, using the changes in eCCl from baseline eCCl and decrease in UOP. The pRIFLE criteria for AKI classified patients' grade of AKI based on changes in eCCl and UOP: pRIFLE R ("Risk") denotes a ≥25% decrease in eCCl or UOP <0.5 ml/kg/h for 8 h; pRIFLE I ("Injury") denotes a ≥50% decrease in eCCl or UOP <0.5 ml/kg/h for 16 h and pRIFLE F ("Failure") denotes a 75% decrease in eCCl from baseline renal function or UOP <0.3 ml/kg/h for 24 h or anuria for 12 h.

The first occurrence of AKI using pRIFLE criteria (based on either UOP or calculated eCCl whichever worst) was noted, and the worst pRIFLE stratum (pRIFLE max) attained in the first 10 days of study enrolment was also recorded.

Patients were classified into two groups AKI and no AKI using modified pRIFLE criteria and risk factors (Table 2) were identified and compared.

Table 1: Current pRIFLE criteria used for diagnosis of AKI[4]

pRIFLE	eCCl	UOP
R - Risk	eCCl>25%	<0.5 ml/kg/h for 8 h
I - Injury	eCCl>50%	<0.5 ml/kg/h for 16 h
F - Failure	eCCl>75% or	<0.3 ml/kg/h for 24 h
L - Loss	eCCl<35 ml/min/1.73 m^2	Or anuria for 12 h
E - End stage	Persistent failure>4 weeks	
	Persistent failure>3 months	

eCCl determined by the Schwartz formula: eCCl=CLCR = (k×Ht)/Serum Cr., where Ht height/length is in cm, serum creatinine in mg/dl and k is a constant (k=0.55 for all children except infants and k=0.45 for infants). GFR: Glomerular filtration rate, SCr: Serum creatinine concentration, eCCl: Estimated creatinine clearance, AKI: Acute kidney injury, pRIFLE: Pediatric Modified Risk, Injury, Failure, Loss, End-Stage Kidney Disease, UOP: Urine output

Table 2: Predictors of AKI using binary logistic regression analysis

Risk factors	No AKI *N*=64 (%)	AKI *N*=50 (%)	Multivariate *P* value	Adjusted OR	95% CI
Length of stay in PICU>4 days	38 (59.4)	41 (82)	0.163	2.112	0.73-6.035
PRISM≤10	32 (50)	38 (76)	0.142	2.036	0.788-5.25
Number days on mechanical ventilation≥4 days	14 (21.9)	25 (50)	0.244	1.806	0.66-4.89
Use of diuretics	57 (89.1)	37 (74)	0.047**	0.324	0.107-0.85
Nor-adrenalin used	28 (43.8)	28 (43.8)	0.718	1.171	0.49-2.74
OR: Odds ratio=OR=ad/bc					
OR<1: Negatively related					
OR=1: Not related					
OR>1: positively related					

PRISM: Pediatric risk of mortality, MODS: Multiorgan dysfunction syndrome

Statistical Methods

Descriptive statistical analysis has been performed in this study. Results on continuous measurements are presented on mean ± standard deviation (SD) (Min-Max), and those on categorical measurements are presented in *N* (%). Significance is assessed at 5% level of significance. Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two groups.[12-15]

RESULTS

Out of 127 patients, 114 enrolled in the prospective pRIFLE validation study had urine specimens and SCr available for analysis. Five patients were excluded because they had less than two SCr levels drawn and eight patients had no urine sample available. Out of total 114 patients, 50 developed AKI and 64 patients (56.2%) did not develop AKI during the study period and served as controls; 23 patients (20.1%) developed pRIFLEmax R AKI; 15 (13.1%) pRIFLEmax I and 12 (10.5%) pRIFLEmax F AKI (Table 3).

Table 3: Incidence of AKI according to modified pRIFLE criteria

Classification	pRIFLE (UOP+Creat) *N*=114 (%)
No AKI	64 (56.2)
AKI	50 (43.8)
Risk	23 (20.1)
Injury	15 (13.1)
Failure	12 (10.5)

AKI: Acute kidney injury, pRIFLE: Pediatric Modified Risk, Injury, Failure, Loss, End-Stage Kidney Disease, UOP: Urine output

Patients were classified into two groups, i.e., AKI and no AKI and baseline characteristics in both the groups were compared.

There were 35 male patients in AKI and 41 in non AKI group. The mean ± SD age of entire cohort was 4.2 ± 4.8 years range (1 month-16 years). Mean age of children in AKI group was 3.2 ± 3.6, whereas mean age in Non AKI group was 4.96 ± 5.02.

The mean ± SD weight of entire cohort was 16 ± 17.8 years range (10-36 kg). Mean weight of children in AKI group was 11.2 ± 12.6, whereas mean weight in non AKI group was 17 ± 18.02.

Risk Factors for AKI

Univariate analysis was performed to identify risk factors for AKI (Table 4). Out of 16 only three risk factors, i.e., duration of PICU stay, higher PRISM score and prolonged ventilator support were strongly significant ($P < 0.01$), and two suspected risks factors, i.e., use of nor adrenaline and diuretics were moderately significant ($P = 0.01 < P < 0.05$) (Figure 1).

Subsequently multivariate logistic regression analysis (Table 2) was performed to identify independent risk factor for AKI which showed following results: Duration of PICU stay >4 days (82% vs. 59.4%, $P = 0.163$, odds ratio [OR] of 2.112, and 95% confidence interval [CI] [0.73-6.035]), PRISM >10 (76% vs. 50%, $P = 0.142$, OR of 2.036, 95% CI: 0.788-5.25), prolonged ventilation (50% vs. 21.9%, $P = 0.244$, OR of 1.806, 95% CI: 0.66-4.89) and use of nor adrenalin (28% vs. 28%, $P = 0.718$, OR of 1.171, 95% CI: 0.49-2.74) were found to have no relation with AKI whereas use of diuretics had negative correlation with AKI (89.1% vs. 74%, $P = 0.047$, OR of 0.324, 95% CI: 0.107-0.85) hence protective role in AKI.

DISCUSSION

Our single-center study evaluates the role of various factors in the development of AKI in PICU. This study shows that the incidence of AKI in PICU is 43.3% which is comparable with the other studies. Cerda J *et al.* reported that AKI affects approximately 35% of intensive care patients and 4-7% of all hospitalized patients.[5]

Table 4: Risk factors of AKI by univariate analysis

Risk factors	AKI *N*=50 (%)	No AKI *N*=64 (%)	*P* value
Age ≤1 years	40.0	21.9	0.124
Male	70	64.1	0.505
Weight<10 kg	26.6	26.6	0.128
Length of stay in PICU>4 days	82.0	59.4	0.009**
Pre-existing illness	24.0	18.8	0.495
PRISM III score>10	76.0	50.0	0.005**
Need for mechanical ventilation	72.0	73.4	0.864
≥4 days of ventilation	50.0	21.9	0.002**
Nor-adrenalin used	56	43.8	0.036*
Liposomal amphotericin used	12.0	3.1	0.136
Antiviral used (acyclovir)	46.0	29.7	0.073+
Use of diuretics	74.0	89.1	0.036*
Use of IV radiocontrast	68.0	65.6	0.790
Blood products used	46.0	42.2	0.684
Infections	34.4	28.0	0.467
MODS	1.6	8.0	0.167

IV: Intravenous, Significant figures: +Suggestive significance (*P*: 0.05<*P* < 0.10), *Moderately significant (*P*: 0.01<*P* < 0.05), **Strongly significant (*P*<0.01). MODS: Multiorgan dysfunction syndrome, PICU: Pediatric intensive care unit, PRISM: Pediatric risk of mortality score, AKI: Acute kidney injury

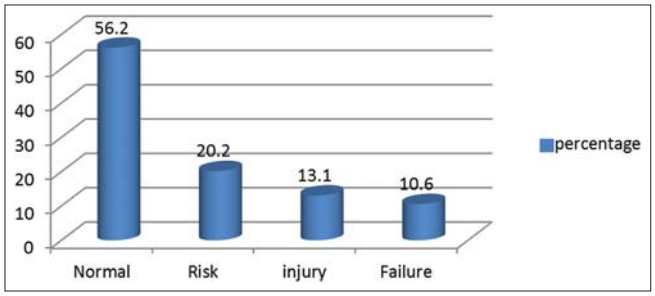

Figure 1: Incidence of acute kidney injury Pediatric Modified Risk, Injury, Failure, Loss, End-Stage Kidney Disease (urine output + creatinine)

The high prevalence of AKI on admission to PICU in our sample 50 out of 114 (42%) suggests that study of risk factors (clinical and biochemical) for developing AKI, may need to include data from patients before ICU admission.

On comparison of AKI and no AKI group, the age, weight, and gender were almost similar and found statistically insignificant ($P > 0.05$). The duration of PICU stay (>4 days), PRISM score >10, and prolonged need for mechanical ventilation >4 days was strongly significant ($P > 0.01$), use of nor-adrenalin, liposomal amphotericin, diuretics were moderately significant risk factors for AKI ($P < 0.05$).

However, binary logistic regression analysis showed that use of diuretics had a protective role (89.1% vs. 74%, $P = 0.047$, OR of 0.324, 95% CI: 0.107-0.85), whereas other factors had no role for the development of AKI in PICU however further studies need to be done to describe its role and benefit in critical patients.

Pre-existing illness, use of blood products, use of IV radiocontrast were also statistically insignificant risk factors ($P > 0.05$).

Potential limitations of our study include the relatively small sample size of 114; another potential concern is the use of an assumed baseline eCCl of 100 ml/min/1.73 m^2 for patients without a known baseline creatinine, in about one-fourth of the patients. The potential danger of this assumption would be to misdiagnose a patient with AKI based on a relative decrease in eCCl if, in fact, the patient had chronic kidney disease. Whether or not such misdiagnosis would lead to unnecessary evaluation or treatment is currently not known, but clinicians should exercise caution when classifying patients with AKI using pRIFLE, or any system using eCCl change when a baseline creatinine level is unknown.[9-15]

CONCLUSION

We conclude that multidimensional AKI classification and stratification systems, such as pRIFLE, can serve well to improve understanding of AKI epidemiology and potentially optimize evaluation and treatment for AKI in children.

Furthermore, as SCr and UOP seem to be late markers of renal injury, use of classification systems will be essential to assess the potential utility of urine and other serum biomarkers to detect AKI earlier, identify risk factors, and direct therapies to prevent or mitigate AKI in children before a rise in SCr concentration.

The global knowledge of the factors involved in the onset and prognoses of AKI is of fundamental importance regarding the management of critically ill patients hence this study found to be useful in predicting and managing AKI early and prevent the subsequent morbidity and mortality due to AKI and its complications.

We also suggest that use of diuretics in critically ill children is a protective factor of AKI, however, further studies need to be done to describe its role and benefit in critical patients.

Information on the overall incidence of AKI based on pRIFLE classification system, risk factors for AKI and the influence of AKI on outcome which occurs later for e.g., ESRD in pediatric patients may be useful in the design of larger multicenter trials to determine the contribution of AKI to patients' long-term morbidity and mortality which is not done in our study and to evaluate the effect of early initiation of aggressive measures to prevent and treat AKI in pediatric ICU patients.

ACKNOWLEDGMENT

I am thankful to almighty and my family. Also thankful to Dr. Shashank Pandey, Dr. Rajeev Agrawal, Dr. Supraja Chandrashekar, Dr. Chetan Dr. Ravi, Dr. Pawan Ghanghoria, Dr. Avyact Agrawal, Dr. Mangilal, Mr. Shishir Pandey, Mr. Rashid for their kind support.

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How to cite this article: Pathak S, Pandey S, Lazarus M. Acute Kidney Injury according to Modified Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease Criteria in the Pediatric Intensive Care Unit: Risk Factors. Int J Sci Stud 2017;4(10):137-141.

Source of Support: Nil, **Conflict of Interest:** None declared.