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"Profile & outcome of Acute Kidney Injury in children admitted to PICU"

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Abstract:
Background: *Acute kidney injury (AKI) is defined as an abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes characterized by a decrease in glomerular filtration rate (GFR). AKI is common in critically ill children and an early diagnosis is important for better outcome.* ***Methods:*** *We conducted a prospective observational study over 2 years at PICU of a tertiary care hospital, NMCH Patna including critically ill children of age group >30 days to 16 years. Children were diagnosed as AKI and its severity categorized, either at admission or subsequently during the hospital stay based on pRIFLE criteria. Clinical variables and outcome were documented to identify the number, timings, risk factors and outcome of AKI.* ***Results:*** *Total 332 subjects were enrolled in the study out of which 84(25.3%) children suffered from AKI. Most (56%) of these cases were in risk category and only 21.4% reached failure stage. Almost 85% of such children suffered from AKI within first 24 hours of admission while 95% developed AKI within 72 hrs. Admission diagnoses of sepsis, shock or pneumonia was significantly more common in patients with AKI. Lower mean age, sepsis, shock, MODS and a higher PRISM score at admission were found to the important risk factors of AKI. Total days of PICU stay (mean 4.7 vs 4.1) and hospital stay (mean 7.8 vs 6.9) was significantly higher in patients with AKI. There was no significant difference in mortality between the two groups. With increasing severity of AKI, there was increase in the duration of PICU stay as well as hospitalization. Similarly, when mortality was studied, there was a progressive and significant increase in mortality with increasing pRIFLE class i.e. 6.4% for risk, 31.6% for injury, and 55.6% for failure patients (P <0.05 for trend).* ***Conclusion:*** *AKI is a significant problem in critically ill children. Most of such children suffer from AKI by 72 hours of PICU admission. Lower age, higher PRISM score, sepsis, shock and MODS were independent risk factors for AKI. Though AKI per se doesn't lead to increased mortality in PICU, it does lead to significantly longer PICU and hospital stay, making it a major burden on our already overwhelmed healthcare system. Higher the severity of AKI, more is the mortality as well as length of PICU and hospital stay.*

Keywords: *Acute kidney injury, mortality, risk actors, Pediatric intensive care unit, pRIFLE*

Abbreviations: *AKI: Acute kidney injury; PICU: Pediatric intensive care unit; PRISM: Pediatric risk of mortality, pRIFLE: pediatric modification of RIFLE(Risk, injury, failure, loss, end stage)*

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I. Introduction:

Acute kidney injury (AKI), formerly called acute renal failure (ARF), is a clinical syndrome where an acute deterioration in renal function results in the inability of the kidneys to maintain fluid and electrolyte homeostasis. It is defined as an abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes characterized by a decrease in glomerular filtration rate (GFR) & an increase in serum creatinine[1]. This is a common entity in critically ill children admitted to paediatric intensive care unit (PICU) and is a significant contributor to morbidity and mortality[2,3]. Though serum creatinine is used as a marker for kidney damage, it is not sensitive for early detection of AKI as it increases when kidneys are already damaged significantly and thus misses the most critical part in early identification and management of AKI in phase of reversibility.[4] Urine output is considered a sensitive index for kidney function and marker for tubular injury. However, the relationship between urine output, GFR and tubular injury is complex and in conditions such as hypotension and volume depletion urine output decreases despite normal tubular function. On the other hand, in nonoliguric renal failure, urine output can be normal in presence of significant tubular damage. GFR is best accepted overall index of kidney function. Estimated GFR is calculated by modified

Schwartz formula. Researchers have confirmed that pediatric modification of RIFLE criteria (pRIFLE, table 1) can be used to detect AKI & its severity early in sick children[5]. AKI occurs early in course of PICU stay (commonly within 7 days of admission) and children who do not suffer from AKI in the first week are unlikely to get it later.[6] In addition, children who do not show improvement in renal status within 24-48 hours of PICU admission are at a high risk of requiring renal replacement therapy. However, there is paucity of data regarding AKI in Indian children, extrapolation of results of western researchers to developing countries may not be valid.[7] As a result, there is pressing need to study AKI in Indian children so as to develop strategies for its prevention and timely intervention. It is quite obvious that the lack of early identification and treatment in many cases means that patients often do not receive essential care before it is too late.

With this background and keeping in mind that most of the Indian studies were retrospective in design which might have distorted the results, we aimed to prospectively determine the incidence, risk factors & outcome of AKI in critically ill Indian children admitted to the PICU of a tertiary care hospital.

Table 1: The modified pediatric version of the rifle criteria (pRIFLE).

Category	Estimated creatinine clearance(ml/min/1.73m2)	Urine output
Risk (R)	Decrease by 25%	< 0.5 mL/kg/hr for 8 h
Injury (I)	Decrease by 50%	< 0.5 mL/kg/hr for 16 h
Failure (F)	Decrease by 75% or or < 35 mL/min/1.73 m2	< 0.3 mL/kg/hr for 24 hr or anuric for 12 hour
Loss (L)	Loss of renal function > 4 weeks	
End stage (E)	End stage renal disease	

II. Aim and Objectives

Aim: To study AKI in sick children admitted to the PICU of a tertiary care hospital.
Objectives: To know the incidence, severity, risk actors and outcome of AKI in such children.

III. Methodology

Study setting: P.I.C.U of Deptt of Pediatrics N.M.C.H Patna
Study duration: 2 years, from April 2018 to March 2020.
Study design: Prospective observational study.
Inclusion criteria: Sick children of age >30 days to <16 years admitted to PICU & staying for >24 hours.
Exclusion criteria: Children with eGFR below 15 ml per minute per 1.73 m2 of body surface area, Known cases of chronic kidney disease, patient on dialysis or receipt of kidney transplant were excluded.
Data Collection: After obtaining written informed consent, cases were enrolled in this study. Information regarding baseline characteristics, detailed relevant history, clinical examination, admission diagnosis was recorded in a structured proforma. Serum creatinine was analyzed with modified Jaffe method and estimated creatinine clearance (eCCl) was calculated according to modified Schwartz formula. Normal renal clearance value of 120 ml/min/1.73 m2 was considered as reference. Other relevant lab investigations were done as per clinical scenario and pertaining findings recorded. AKI was defined and categorized based on pRIFLE criteria either at admission or subsequently during the hospital stay and the maximum pRIFLE stage reached during PICU stay was noted. Special attention was given on collecting information about the primary disease or condition, PRISM score[8], use of nephrotoxic drugs, inotropic support, mechanical ventilation, dialysis, mortality and the total length of PICU and hospital stay.
Statistical analysis: Pertaining data was entered in Microsoft excel and analyzed by SPSS version 19 software. Dichotomous events were analyzed by Chi-Square test. Continuous variables were compared by Student t-test. P value less than 0.05 was considered significant. Univariate and multivariate logistic regression analysis was done for study of association.

IV. Results

Total number of PICU admissions over the 2 year period was 361, out of which 29 were excluded. So, the study population here was 332. Among these, 84(25.3%) children suffered from AKI according to pRIFLE staging. As shown in Table 2, most (56%) of these cases were in risk category and only 21.4% reached failure stage. We didn't get any case in renal loss or end stage renal disease category.

Table 2: AKI cases according to degree of severity as per pRIFLE classification.

AKI severity	Number	Percentage
Risk category	47	55.9
Injury category	19	22.6
Failure category	18	21.4
Loss	0	0
End stage renal disease	0	0

Time of onset of AKI: 71 of 84 patients (84.5%) had AKI within 24 hours of admission while 80 (95%) patients developed AKI within 72 h. The maximum time for presentation of AKI was 8 days in our study.

Baseline characteristics: On comparing the two cohorts, we found that those children who suffered from AKI had lower mean age & a significantly higher PRISM score at admission.

Table 3: Comparison of baseline characteristics of patients in the AKI and non-AKI groups

Characteristic	Children with AKI, n=84	Children without AKI, n=248	p value
Age: mean (SD)	2.89 (3.12)	4.17 (3.95)	0.007
Male gender	49; 58.3%	158; 63.7%	0.49
PRISM score:Mean (SD)	6.12 (4.2)	4.09 (3.58)	0.001

AKI and primary condition at admission: Among the children with AKI, 52(61.9%) had infectious etiology. Pneumonia constituted 25% & tropical febrile illnesses (dengue, malaria) constituted 7.14% of all AKI patients. Sepsis (without localizing signs) was seen in 12 (14.3%) cases. Overall, 16 cases had a positive blood culture: Staphylococcus aureus (3), Streptococcus pneumoniae (4). Pseudomonas aeruginosa (2), Escherichia coli (2), Klebsiella pneumoniae (4), Enterococcus species(1). Diagnoses with sepsis, shock or pneumonia at PICU admission was significantly more common in patients with AKI.

Table 4: Comparison of diagnosis at admission of patients in the AKI and non-AKI groups

Diagnosis	AKI group: n(%)	Non AKI group: n (%)	p value
Sepsis	12 (14.3)	15(6.03)	0.02
Shock	18 (21.4)	29(11.7)	0.03
Dengue	5 (5.9)	17(6.8)	0.8
Malaria	1 (1.2)	6(2.4)	0.5
Pneumonia	21 (25%)	34(13.7)	0.02
Cardiac disease	7 (8.3)	22 (8.9)	0.87
Acute Encephalitis syndrome	8 (9.5)	37(14.9)	0.2
Gastroenteritis	8 (9.5)	11(4.4)	0.08
Liver failure	7 (8.3)	22(8.9)	0.9
Meningoencephalitis	5 (5.9)	17(6.8)	0.8
Poisoning	1 (1.2)	16 (6.4)	0.06
Malignancy	2(2.4%)	22 (8.1)	0.07

AKI in relation to PRISM score at admission: Comparison of PRISM score in the pRIFLE subclasses showed that patients with a more severe pRIFLE subclass also had a higher average PRISM III score.

Table 5: pRIFLE subclass and average PRISM score of patients with AKI:

RIFLE subclass	PRISM score: Mean (SD)
Risk (R)	4.98 (2.4)
Injury (I)	6.14 (3.9)
Failure (F)	7.02 (3.820
Non AKI Group	4.09 (3.58)

Risk factors for AKI: We performed univariate analysis to identify risk factors for AKI and found that lower age, shock, sepsis, CHF, coagulopathy, MODS, Mechanical ventilation and use of nephrotoxic drugs were found to be more commonly associated with AKI in univariate analysis. However, in multivariate regression analysis only lower mean age, sepsis, shock, MODS and a higher PRISM score at admission were found to significantly contribute to the development of AKI

Table 6: Risk factors for developing AKI (univariate analysis)

Risk Factors	AKI group	Non- AKI group	p value
Mean age	2.89 (3.12)	4.17 (3.95)	0.007
Shock	22(26.1%)	34(13.7%)	0.009
Sepsis	31(36.9%)	41(16.5%)	0.0002
Cogestive Cardiac failure	14(16.7%)	2(8.9%)	0.048
Coagulopathy	9(10.7%)	6(2.4)	0.002
MODS	34(40.5%)	52(20.9%)	0.0004
Mechanical Ventilation	29(34.5%)	44(17.7%)	0.002
Nephrotoxic drugs	31(36.9%)	63(25.4%)	0.045
PRISM score: Mean (SD)	6.12 (4.2)	4.09 (3.58)	0.0001

Duration of specialized care and mortality: Total days of PICU and hospital stay were significantly higher in patients with AKI as compared to non-AKI patients. Though patients with AKI were more likely to need mechanical ventilation (P =0.002), duration of ventilation was comparable between AKI and non-AKI groups. Also, there was no significant difference in mortality between the two groups.

Table 7: Duration of mechanical ventilation, length of PICU stay, length of hospitalization and mortality in AKI and Non-AKI groups

Variable	AKI group	Non AKI group	p value
Days on Mechaical ventilation: Mean (SD)	4.9 (2.3)	4.4 (2.2)	0.07
Days of PICU stay: Mean (SD)	4.7 (2.8)	4.1 (2.1)	0.04
Days of Hospital stay: Mean (SD)	7.8 (3.4)	6.9 (3.1)	0.026
Mortality	19(22.6%)	36 (14.5%)	0.09

Renal recovery: Children who were shifted out of PICU with abnormal serum creatinine were followed up for renal recovery in ward and in subsequent follow up visits post discharge. 53 (81.5%) out of the surviving 65 patients with AKI had complete renal recovery before discharge. Amongst the patients with persistent renal dysfunction, 19 (22.2%) died in the PICU, 5 (5.9%) developed chronic kidney disease and 4 (4.8%) patients had normalized serum creatinine during follow-up visits by 1 month after discharge. 3 such children didn't turn up for follow up and hence their final status couldn't be ascertained.

Relation between AKI category, duration of treatment & mortality: As expected, with increasing severity of AKI, there was increase in the duration of PICU stay as well as hospitalization. Similarly, when mortality was studied, there was a progressive and significant increase in mortality with increasing pRIFLE class i.e. 6.4% for risk, 31.6% for injury, and 55.6% for failure patients (P <0.05 for trend).

Table 8: Relation between pRIFLE class, length of PICU stay, length of hospitalization & mortality

AKI class	Median duration of PICU stay	Median duration of hospitalisation	Mortality
RISK	3 (range 2-5)	5(range 5-10)	3/47 (6.4%)
INJURY	4(range 3-7)	7(range 5-12)	6/19 (31.6%)
FAILURE	7(range 5-9)	9(range 7-14)	10/18 (55.6%)
Non AKI	6(range 3-9)	8(range 6-12)	36(14.5%)

V. Discussion

The present study is a single-centre study with the objective to study AKI in detail among critically ill pediatric patients. Various researchers have reported incidence of AKI ranging widely from quite low to high (5-70%).[9,10] In their work from northern India, Mehta et al.[11] reported 36.1% incidence of AKI in the critically ill children. Such variability can be partly explained by the variable definitions of AKI incorporated in the studies. Zappitelli et al[12] showed that taking baseline eCCl of 120 ml/min (instead of 100ml/min) and using baseline estimated creatinine clearance (instead of changes in serum creatinine), more patients were diagnosed as having AKI. Here, we have used the pRIFLE criteria using changes in eCCl as the defining criteria and assumed the baseline eCCl to be 120 ml/min. This may have lead to a relatively higher incidence of AKI in the present study.

In our study, nearly 85% children had AKI at admission while 95% developed AKI within 72 hours, similar to the study by Bailey et al.[13] This supports the previous notion that children develop their maximum number of organ failures early in the intensive care unit (ICU) course, unlike the observation in adult patients who develop organ dysfunction late. Most (56%) of the AKI cases were in risk category and only 21.4% reached failure stage. This highlights that most children have a potentially reversible cause of AKI and hence early diagnosis and intervention can lead to a better outcome in children with AKI.

Various researchers have described different risk factors for development of AKI in critically ill children. However, there can be no generalization due to the heterogenisity of the definition and the population studied. While sepsis, glomerulonephritis, HUS and acute tubular necrosis are the major cause in developing countries, these are replaced by hemato-oncologic complications and pulmonary failure in the west. In our study, we found that lower mean age, sepsis, shock, MODS and a higher PRISM score at admission were found to significantly contribute to the development of AKI. This can be attributed to the fact that the sickest children have higher chances of organ injury. This was also evident by our finding that patients with a more severe pRIFLE subclass also had a higher average PRISM III score.

Though some studies have shown that AKI is associated with increased mortality, some have negated this finding[14]. Although crude mortality seemed to be higher in AKI group, this wasn't significant statistically. As expected, we noticed a significant trend of higher mortality with higher AKI stage. Similarly, with increasing severity of AKI, there was increase in the duration of PICU stay as well as hospitalization. Children who survived their illness had excellent renal recovery in our study. This can be partly explained by the early diagnosis and prompt treatment of the primary condition that had led to AKI.

VI. Conclusion

AKI is a significant problem in critically ill children. Most of such children suffer from AKI by 72 hours of PICU admission. Lower age, higher PRISM score, sepsis, shock and MODS were independent risk factors for AKI. Though AKI per se doesn't lead to increased mortality in PICU, it does lead to significantly longer PICU and hospital stay, making it a major burden on our already overwhelmed healthcare system. Higher the severity of AKI, more is the mortality as well as length of PICU and hospital stay.

7. Limitation: First limitation is that ours is a single-centre study. Secondly, we classified patients by pRIFLE criteria, which used a change in eCCL, and if baseline creatinine was unavailable, the patients were assumed to have a normal baseline eCCL of 120 ml/min/1.73 m^2. Though Acute Kidney Injury Network (AKIN) group proposed refinements to the pRIFLE classification to use change in serum creatinine instead of change in eCCL, further studies are required to compare AKIN and pRIFLE in children to determine which system is more consistent and a better predictor.

8.Conflict of Interest: none

9.Financial Disclosure: The authors declare that this study hasn't received any financial support.

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