

Original Research Article

Profile and outcome of acute kidney injury in critically ill children admitted to pediatric intensive care unit

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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) and an increase in serum creatinine. AKI is common in critically ill children and early diagnosis is important for better outcome in these children.

Methods: This was a prospective observational study. Critically ill infants and children of either sex and in age group between >28 days to 12 years admitted to pediatric intensive care unit (PICU) were included. Serum creatinine and estimated creatinine clearance (eCC) were used to and patients classified as AKI on pRIFLE criteria either at admission or subsequently during the hospital stay. AKI cases were further classified into risk, injury or failure category on the day of development of AKI and the maximum pRIFLE stage reached during PICU stay was noted. Detailed data regarding the treatment received and use of nephrotoxic drugs, inotropic support, mechanical ventilation, dialysis and total length of stay in PICU in all was noted. Outcome of the subjects were observed for survival or mortality.

Results: Total 343 subjects were enrolled in the study. During the study 27.1% patients developed AKI according to pRIFLE staging. In AKI category 60.21% reached maximum risk category, 21.5% reached maximum injury category, 18.28% reached maximum failure category. Amongst AKI subjects 64.52% had infectious etiology. Multiorgan dysfunction, encephalopathy, shock, metabolic acidosis, hypertension, mechanical ventilation and nephrotoxic drugs administration were more associated with AKI and was statistically significant.

Conclusions: Pediatric modification of RIFLE criteria is sensitive index to detect AKI at earliest in critically ill children for early intervention leading to better outcome.

Keywords: AKI, MODS, pRIFLE, Sepsis

INTRODUCTION

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) and an increase in serum creatinine.¹ AKI is common in critically ill children admitted to paediatric intensive care unit and is associated with increased morbidity and mortality.^{2,3}

There is large variations in incidence of AKI in critically ill children in Pediatric Intensive Care Unit (PICU), depending on study population, risk factor, regional and environmental differences.^{4,5} Recently term acute renal failure (ARF) is replaced by AKI to provide uniformity of definition and to standardize care of patients.⁶

Serum creatinine is used as a marker for kidney damage, but it is insensitive marker for early detection of AKI.

Serum creatinine increases when kidneys are already damaged significantly and miss the most critical part in early identification and management of AKI in phase of reversibility.³ Urine output is sensitive index for kidney function and marker for tubular injury but the relationship between urine output, GFR and tubular injury is complex. In conditions such as hypotension and volume depletion urine output decreases inspite of normal tubular function in contrast to nonoliguric renal failure where 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. The RIFLE criteria developed by the Acute Dialysis Quality Initiative Group, consist of acronym for the three-grade level of injury (risk, injury and failure)

based on the degree of elevation in serum creatinine or urine output and two outcome measures (loss and end stage renal disease).¹

The RIFLE was later modified in 2007 using the “Acute Kidney Injury Network (AKIN)” criteria.⁶ Refining further AKIN group replaced the categories of risk, injury, and failure to Stages 1, 2 and 3, respectively, and the outcome categories loss and end-stage renal disease were eliminated. An absolute increase in serum creatinine levels of at least 26.5 $\mu\text{mol/L}$ (0.3 mg/dl) has been added to the minimum requirements for Stage 1. Patients starting RRT (Renal Replacement Therapy) are automatically classified as having Stage 3 AKI, regardless of their serum creatinine levels and urine output.

Table 1: The modified pediatric version of the rifle criteria (prifle).⁶

Category	Estimated creatinine clearance*(ml/min/1.73m ²)	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 < 35 mL/min/1.73 m ²	< 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	

Many studies confirmed that paediatric modification Risk, Injury, Failure, and Loss, End-stage Renal Disease-RIFLE criteria (pRIFLE) can be used to detect acute kidney injury earliest as possible in critically ill children in PICU and help to decide severity and progress of AKI and help to take decision regarding starting renal replacement therapy at earliest (Table 1).

AKI classification using pRIFLE criteria shown that AKI is very common in critically ill children in PICU and is associated with significant mortality and morbidity.⁷ pRIFLE served most sensitive criteria to detect AKI at earliest than other criteria and definitions. AKI occurs in very early course in PICU, most often within first 7 days of PICU admission and patients who did not developed AKI in first week are unlikely to develop it later.

In addition patients who did not show improvement in kidney function within 24-48 hours of PICU admission were at greater risk of requiring renal replacement therapy, hence there is need to detect AKI at earliest and institute aggressive measures to prevent and treat AKI. So pRIFLE criteria serve to detect AKI at earliest and help to take decision in management.⁷

METHODS

This was a prospective observational study conducted at PICU of tertiary care teaching hospital over the period of 1 year. Institutional Ethics Committee approval and parents informed consent was obtained prior to

enrollment of study subjects. Critically ill Infants and children of either sex in age group age >28 days to 12 years admitted to PICU and staying for more than 24 hours were included. Patients with estimated GFR below 15 ml per minute per 1.73 m² of body surface area, patient on maintenance dialysis, or receipt of kidney transplant and PICU stay of less than 24 hours were excluded.

Data regarding baseline characteristics, detailed relevant history, clinical examination, admission diagnosis noted in structured proforma. Serum creatinine was analyzed with modified Jaffe method and estimated creatinine clearance (eCC) was calculated according to Schwartz formula. Normal renal clearance value of 120 ml/min/1.73 m² (53) was considered as reference. Other relevant lab investigations findings noted. Patients classified as AKI cases if AKI is diagnosed based on pRIFLE criteria either at admission or subsequently during the hospital stay.

Estimated creatinine clearance criteria of pRIFLE classification was used to classify AKI into risk, injury or failure category on the day of development of AKI and the maximum pRIFLE stage reached during PICU stay was noted.

Detailed data regarding the treatment received and use of nephrotoxic drugs, inotropic support, mechanical ventilation, dialysis was noted. While the subjects were under treatment, the subjects were observed for survival

or mortality. The total length of stay in PICU in all subjects was recorded.

RESULTS

Total 343 subjects were enrolled in the study. Maximum (28.9%) patients were in 3 year to 6-year age group. (Figure 1). During the study 93(27.1%) patients developed acute kidney injury according to pRIFLE staging, giving 27.1 % prevalence of acute kidney injury in study population (Table 2).

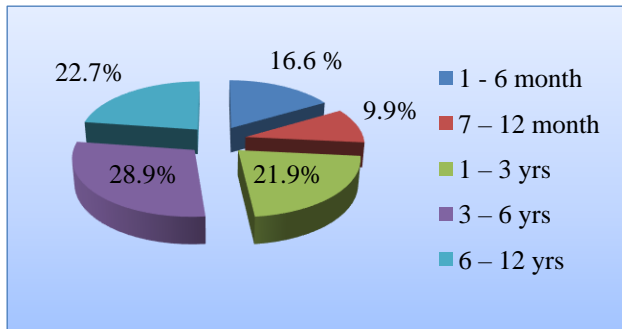


Figure 1: Age wise distribution of cases of AKI.

As shown in Table no. 3, out of 93 patients who developed AKI, 60.21% reached maximum risk category, 21.5% reached maximum injury category, 18.28% reached maximum failure category. We not found any patient in renal loss or end stage renal disease category.

Table 2: Distribution of cases according to presence of acute kidney injury (AKI).

	No. of Cases (n=343)	%
AKI cases	93	27.1%
Non-AKI cases	250	72.9%

Table 3: Distribution of acute kidney injury cases according to degree of severity by pRIFLE classification.

	No. of cases (n=93)	%
Risk category	56	60.21
Injury category	20	21.5
Failure category	17	18.28
Loss	0	0
End stage renal disease	0	0

The Case diagnosis of children with AKI observed is depicted in Figure 2. Out of 93 patients who developed AKI 64.52% had infectious etiology. Pneumonia constituted 18.82% of all AKI cases.

Tropical febrile illnesses (dengue, malaria) constituted 11.83% of AKI patients. Sepsis (without localizing signs) was diagnosed in 19 (22.83%) children, 9 were culture

positive. organisms isolated were *Pseudomonas aeruginosa* (3 patients), *Escherichia coli* (2 patients), *Klebsiella pneumoniae* (3 patients) and *Streptococcus pneumoniae* (1 patient). Other etiologies were underlying cardiac disease, acute post-streptococcal glomerulonephritis (PSGN), malignancy, Hemolytic Uremic Syndrome (D-HUS) and status epilepticus. Among 93 patients who developed AKI 19 patients had a sepsis as etiological factor. Among 19 patients who had sepsis 9 (47.37%) was culture positive with micro-organism profile (Table 4).

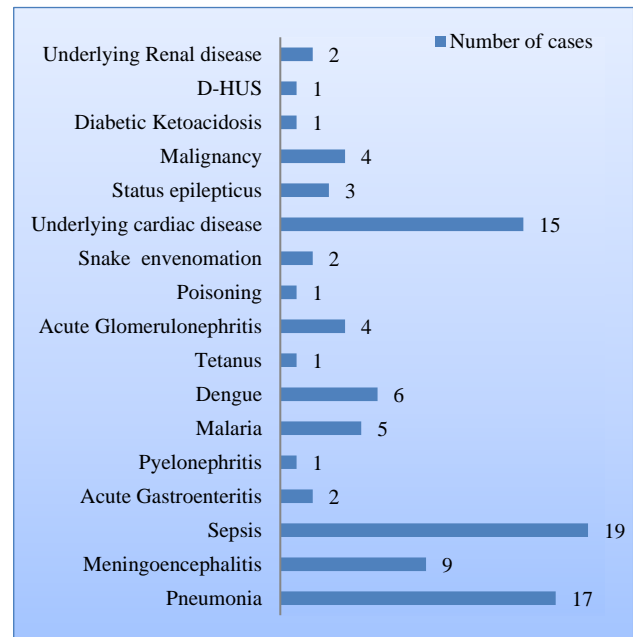


Figure 2: Case diagnosis of children with acute kidney injury (n=93).

As seen from Table 5, median age in AKI group was 20 months while in non-AKI group median age was 45 month and AKI was seen more common in younger age group (p value 0.0005).

Table 4: Distribution of sepsis cases according to culture positivity.

Sepsis cases(n=19)	Number of cases
Culture positive	9 (47.37%)
<i>Pseudomonas aeruginosa</i>	3
<i>Escherichia coli</i>	2
<i>Klebsiella pneumoniae</i>	3
<i>Streptococcus pneumoniae</i>	1
Culture negative	10 (52.63%)

In AKI group, male were 49 (52.69%) and female were 44 (47.31%), while in non-AKI group male were 133(53.2%) and female were 117(46.8%), with nonsignificant p value (0.2169). There was no gender predilection for AKI

Table 5: Clinical and treatment profile of AKI and Non-AKI cases.

Risk -factors	AKI	No AKI	Unadjusted odds ratio	95% C.I.	p-value
Demographic parameter					
Age in month, mean±SD	33.67± 33.56	48.91± 36.75	-	-	0.0005, HS
Median	20 (1-140)	45 (1-144)	-	-	
Gender (M/F)	49/44	133/117	1.35	0.81-2.23	0.2169, NS
Clinical parameter					
MODS	45 (48.39%)	48 (19.2%)	3.94	2.28-6.80	<0.0001, HS
Encephalopathy	33 (35.5%)	45 (18%)	2.50	1.41-4.40	0.0006, HS
Shock	49 (52.6%)	72 (28.8%)	2.75	1.63-4.63	<0.0001, HS
Metabolic acidosis	14 (15.05%)	2	21.97	4.83-201.28	<0.001, HS
Hypertension	7 (7.53%)	0	-	-	<0.001, HS
Treatment related factors					
Vasopressor	41 (44.09%)	96 (38.4%)	1.36	0.75-2.10	0.3392, NS
Mechanical Ventilation	46 (49.46%)	60 (24%)	3.09	1.82-5.26	<0.0001, HS
Nephrotoxic drugs	48 (51.61%)	90 (36%)	1.89	1.13-3.15	0.0088 HS

In the present study among clinical factor; multiorgan dysfunction, encephalopathy, shock, metabolic acidosis, hypertension and among treatment related factor; mechanical ventilation and nephrotoxic drugs administration were significantly present an AKI group with p value <0.05. On univariate analysis risk factor for AKI are younger age, mechanical ventilation, MODS, shock.

Table 6: Multiple logistic regression analysis for risk factors of acute kidney injury.

Risk factor	Adjusted OR	95% CI	p-value
Age	0.98	0.97-0.99	<0.001, HS
Sepsis	2.21	1.06-4.60	0.032, S
MODS	3.94	1.87-8.28	<0.001, HS
Shock	1.84	1.03-3.27	0.038, S

As shown in Table no. 6, on multiple logistic regression analysis, independent risk factor for AKI in PICU in our study found was;

- Age (95% C.I. 0.97-0.99, p value <0.001)
- Multiorgan dysfunction syndrome (95% C.I. 1.87-8.28, p value <0.001)
- Sepsis (95% C.I. 1.06-4.60, p value 0.032)
- Shock (95% C.I. 1.03-3.27, p value 0.038)

In our study, dialysis requirement was more in AKI with sepsis (63.16%) than AKI without sepsis (8.1%) with p value of <0.0001 (Table 7).

We compared demographic, clinical treatment related factors among non-survivor and survivor in AKI group. (Table 8). In both group median age was 20 month and there was no gender predilection. Multiorgan dysfunction, requirement of renal replacement therapy,

metabolic acidosis, requirement of mechanical ventilation significantly present in non-survivor group as compared to survivor group, with p value <0.05.

Table 7: Profile of children with AKI requiring dialysis with respect to presence or absence of sepsis.

	Need for dialysis		p-value
	Yes	No	
AKI with sepsis (n=19)	12 (63.16%)	7 (36.84%)	Chi2=29.9295 P<0.0001, HS
AKI without sepsis (n=74)	6 (8.1%)	68 (91.89%)	

The predictors of mortality in AKI group on univariate analysis were, requirement of mechanical ventilation, MODS, requirement of renal replacement therapy and metabolic acidosis, with p value of <0.05.

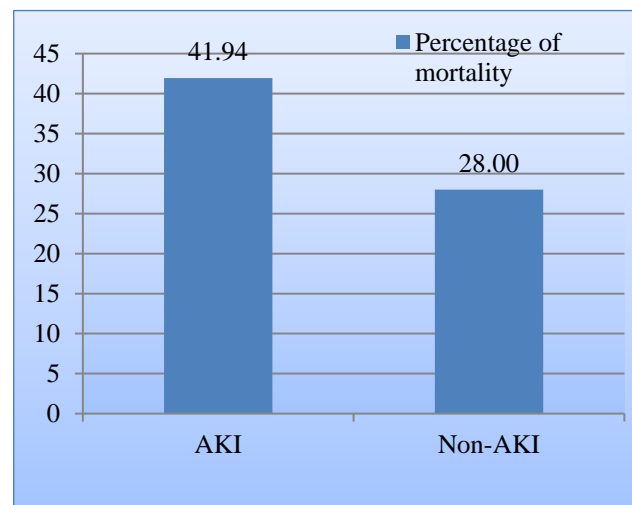


Figure 3: Mortality profile in AKI and non-AKI group.

In multivariate analysis, only mechanical ventilation (OR 12.82, 95% CI 3.74-43.94, P = 0.0001), MODS (OR 3.67, 95% CI 1.12-12.07, P < 0.032) were found to be

independent predictor for mortality in AKI group (Table no. 9).

Table 8: Predictor of mortality among survivor and non-survivor children with AKI.

	Non-survivor	Survivors	p-value
Demographic factors			
Age (month), mean±SD	32.87±32.73	34.24±34.45	0.9845, NS
median	20 (1-120)	20 (1-144)	
Gender (Male/Female)	24/15	25/29	0.146, NS
Clinical factors			
MODS	32 (82.05%)	13 (24.07%)	<0.0001, HS
Renal replacement therapy	13 (33.34%)	5 (9.25%)	<0.0001, HS
Length of stay(days) mean±SD	4.79 ±2.02	5.27±2.50	0.3242, NS
Encephalopathy	18 (46.15%)	15 (27.78%)	0.068, NS
Shock	22 (56.41%)	27 (50%)	0.107, NS
Metabolic Acidosis	14 (35.9%)	0	<0.000, HS
Hypertension	2 (5.13%)	5 (9.25%)	0.456, NS
Risk category	18	38	0.019, S
Injury category	9	11	0.754, NS
Failure category	12	5	0.008, HS
Treatment related factor			
Vasopressor requirement	21 (53.85%)	20 (37.04%)	0.107, NS
Requirement of Mechanical Ventilation	39 (100%)	7 (12.96%)	<0.0001, HS
Nephrotoxic drug administration	20 (51.28%)	28 (51.85%)	0.957, NS

Mortality in patients with AKI is 41.94% which was higher than in non-AKI group (28%) (Figure 3).

Table 9: Multiple logistic regression analysis for predictors of mortality in patients with acute kidney injury.

Variable	Adjusted odds ratio	95% Confidence interval	p-value
Mechanical ventilator	12.82	3.74 - 43.94	<0.0001, HS
MODS	3.67	1.12 - 12.07	0.032, S

In AKI group mortality is significantly high in failure category (70.59%), as compared to injury category (45%) which is more than that in risk category (32.14%) (Figure 4).

Table 10: Profile of non-surviving children with AKI with respect to presence or absence of sepsis.

	Mortality		p-value
	Yes	No	
AKI with sepsis (N=19)	12 (63.16%)	7 (36.84%)	Chi ² = 4.4167 P = 0.036, S
AKI without sepsis (N=74)	27 (36.49%)	47 (63.51%)	

Mortality in acute kidney injury patients with sepsis was higher (63.16%) than in AKI patients without sepsis (36.49%) with p value of 0.036 (Table 10).

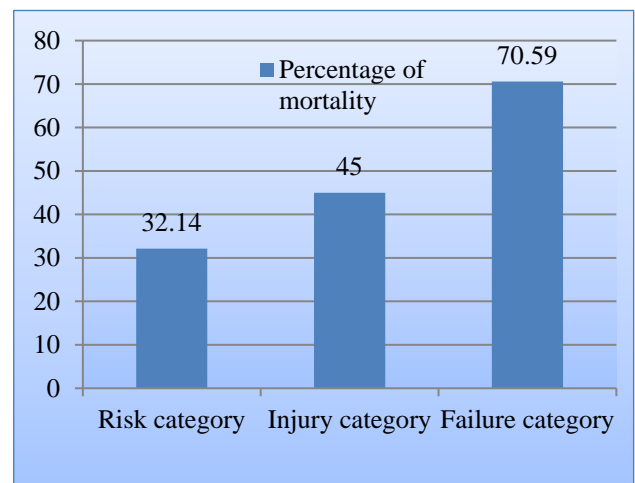


Figure 4: Mortality according to severity of acute kidney injury.

In the present study, we observed that out of 93 patients 44 (47.31%) patients had AKI within 24 hours of PICU, and most cases of AKI (63.44%) reached maximum pRIFLE stage within 72 hours of PICU admission (Table 11).

Table 11: Time of AKI development.

Time of AKI development	Risk category	Injury category	Failure category	Any AKI
<24 hour	24	11	9	44 (47.31%)
24hour-72hour	11	1	3	15 (16.13%)
>72 hour	21	8	5	34 (36.56%)

Renal replacement therapy requirement was more in failure category (16 patients out of 17; 94.18%) than injury and risk category (Table 12).

Table 12: Association of severity of AKI and renal replacement therapy.

RRT	AKI category		
	Risk	Injury	Failure
Yes (18)	1 (1.79%)	1 (5%)	16 (94.18%)
No (75)	55	19	1
Total	56	20	17
p value	<0.001	0.107NS	<0.001HS

Table 15: Association of RIFLE staging and length of stay in hospital.

Length of stay (days)	RIFLE staging			p-value
	Risk	Injury	Failure	
Mean±SD	4.26±1.11	5.7±1.59	7.0±4.10	F = 12.47; P <0.001, HS

In patients with AKI the length of stay in PICU was 5.07±2.31 days which was higher than length of stay of patients without AKI it was 4.4±2.14days (Table 14).

The Length of stay in PICU was also increased as the severity of AKI, with maximum length of stay in failure category(7±4.1days) as compared to injury(5.7±1.59days) and risk category(4.26±1.11days) with p value of <0.001. (Table 15).

DISCUSSION

This study is single centre prospective observational study from a tertiary care center in central India with the objective to determine prevalence of AKI in critically ill children admitted to PICU, risk factor for AKI in PICU and predictor of mortality. Knowing etiological profile and outcome of AKI is helpful to detect AKI early and intervene early.

Few studies in India conducted on epidemiology of AKI in critically ill children in PICU, incidence was ranging from 10 to 82% depending on differences in study population, regional variation and study design.⁷⁻⁹ Ackan arickan et al found incidence of 82% in critically ill children in PICU using modified pRIFLE criteria. Ahmad

Multiorgan dysfunction associated with all patients in failure category.

Table 13: Association of RIFLE staging and multiorgan dysfunction.

MODS	RIFLE staging			p-value
	Risk (%)	Injury	Failure	
Yes	11 (19.64)	17 (85%)	17 (100%)	Chi ² = 47.3954 P <0.001 HS
No	45	3	0	

While in injury category 85% patients had associated multiorgan dysfunction.

Table 14: Length of stay in PICU of patients with AKI and non-AKI.

Length of stay (days)	Patients with AKI	Patients without AKI	P value
Mean±SD	5.07±2.31	4.4±2.14	0.013S

In risk category only 20% patients had multiorgan dysfunction (Table 13).

Kaddourah et al found that out of total 4683 patients evaluated, AKI developed in 1261 (26.9%) patients.^{7,10}

The different incidence of AKI in PICU my attribute to multiple definitions of AKI used. Zappitelli et al proved that using baseline estimated creatinine clearance (eCCL) estimates higher incidence of AKI than using changes in baseline serum creatinine.¹¹ They also showed that assuming a baseline eCCL of 120 ml/min was also associated with higher incidence of AKI compared to assuming 100 ml/min as baseline eCCL. In our study we used the pRIFLE classification scheme using change-estimated creatinine clearance as defining criteria and assumed a baseline eCCL of 120 ml/min. We found the prevalence of AKI to be 27.1% in critically ill-children admitted to the PICU.

In our study, we studied severity grading of AKI cases according to pRIFLE criteria, we found that 60.2%, 21.5%, 18.28% patients were in risk category, injury category, and failure category, respectively. In a study by Mehta et al, maximum cases of AKI had Stage 1 (65.8%), followed by Stage 2 (17.8%) and Stage 3 (16.4%). Similar pattern of AKI level (risk, injury, failure) was reported by Akcan-Arikan et al, i.e, 48.8%, 26%, 25.2%, and plotz et al, i.e, 52%, 37%, 11% respectively.^{7,9,12}

In the present study, 63.5% of patients developed AKI within 72 h of PICU stay Plotz et al identified 36.2% and 45% of AKI on day first of admission, respectively, in comparison to the present study in which 47% had AKI on first day of admission.

Akcan-Arikan et al also identified that AKI was either present on admission or does develop early in the course of intensive care emphasizing the importance of early diagnosis of AKI.^{12,7}

A wide spectrum of etiologies for AKI has been found in studies across the world. While sepsis, glomerulonephritis, HUS and acute tubular necrosis predominate in developing countries, these have been replaced by hemato-oncologic complications and pulmonary failure as causes of AKI in the west.^{13,14}

In India Shweta Naik et al found Sepsis, gastroenteritis, status epilepticus, bronchopneumonia and central nervous system infections were more common etiology in patients with AKI.¹⁵

In our study; we found that the common etiologies of AKI in critically ill children admitted to PICU were infections, PSGN, underlying heart diseases. Pneumonia, sepsis and meningoenephalitis accounted for the majority of all infections. Pneumonia and sepsis made up around 60% of all infections associated with AKI and were associated with high mortality.

Increased risk of developing AKI has been mentioned with pneumonia but seems to have been under-reported in children.¹⁶ In a prospective study from Scotland, out of 1241 adults with pneumonia, 18% had AKI.¹⁷ Tropical febrile illnesses have been significantly associated with AKI, especially in adults.¹⁸ In our study too, tropical febrile illnesses (dengue and malaria) constituted 9.3% of children with AKI.

Various studies have attempted to identify risk factors for development of AKI in critically ill children. Mehta et al found that younger age, shock, sepsis and need for mechanical ventilation were independent risk factors for AKI in their cohort.⁹ According to Slater MB et al, Patients at high risk for development of acute kidney injury included those urgently admitted to the ICU, who developed respiratory dysfunction during their ICU care, and those who treated with extracorporeal membrane oxygenation.¹⁹

The single greatest risk factor for acute kidney injury was the administration of nephrotoxic medications during ICU admission. In our study on multiple logistic regression analysis younger age, presence of MODS, sepsis and shock were found to be risk factor of AKI.

The mortality in AKI in children reported to vary from 16% to 43.8%.^{7,20,21} In the present study, it was 41.94%,

which is comparable to a recent study from southern India reporting 46% mortality.²

In the present study, the mortality in patients with AKI (41.94%) was higher than mortality in patients without AKI (28%). We also observed that mortality increases as the severity of AKI increases according to pRIFLE classification. The mortality in failure category (70.59%) was much higher than injury (45%) and risk (32.14%) category. We also noticed that mortality in acute kidney injury patients with sepsis is higher (63.16%) than in AKI patients without sepsis (36.49%) with p value of 0.036. Similar finding noticed by Marilla et al that sepsis is independent predictor of death.²²

In our study, requirement of mechanical ventilation was found to be an independent predictor of mortality in critically ill children admitted in PICU with AKI. Though MODS, requirement of renal replacement therapy and metabolic acidosis predicted mortality on univariate analysis, they were eliminated on multivariate logistic regression analysis.

Mortality in AKI is primarily related to aetiology; PSGN and gastroenteritis having a much better outcome than sepsis, malignancy.²³ Sepsis and AKI in failure category have been associated with more mortality. In critically ill-patients with AKI undergoing haemodialysis, cardiovascular co-morbidities, metabolic acidosis and acute respiratory distress syndrome led to poor outcome.²⁴

CONCLUSION

From the present study we concluded that prevalence of AKI in critically ill children admitted to PICU was 27.1%. The etiological profile of AKI was dominated by infections, including pneumonia, sepsis, meningoenephalitis and tropical febrile illnesses. PSGN, congestive cardiac failure also contributed significantly. The mortality in critically ill children admitted to PICU in children with AKI was higher than mortality in children without AKI.

Mortality also increased as severity of AKI increased with maximum mortality in failure category followed by injury and risk category. The length of stay in PICU also increased in patients with AKI, it also increased as kidney injury progressed with maximum length of stay in failure category. Requirement of mechanical ventilation was found to be an independent predictor of mortality in children with AKI. Pediatric modification of RIFLE criteria is sensitive index to detect AKI at earliest in critically ill children for early intervention leading to better outcome in these children.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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