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Study of Acute Kidney Injury in Critically Ill Children Admitted To Paediatric Intensive Care Unit of a Tertiary Centre

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ABSTRACT: *Acute Kidney Injury (AKI) refers to a reversible accumulation of urea, creatinine and nitrogenous waste products and disturbances in maintenance of fluid and electrolyte homeostasis. The incidence of AKI continues to increase in the Paediatric age group particularly in critically ill children with the etiology shifting from primary renal disorders to multifactorial cause. A prospective observational study was done with 342 children aged between 1-12 years, admitted in Paediatric Intensive Care Unit (PICU) of Institute of Child Health & Research Centre, Madurai Medical College, Madurai during July 2015 to June 2016. Aim of the study was to determine the incidence, clinical profile and outcome of AKI in critically ill children using AKIN staging. The overall incidence of AKI among critically ill children was 31%. The mortality rate was 42.5% and 19.7% patients with AKI had partial renal recovery at the time of discharge. 26.4% patients required renal replacement therapy (RRT). Infectious causes 56.6% (Sepsis, Meningoencephalitis, Bronchopneumonia) dominated the etiological profile. Incidence of AKI is high in critically-ill children. AKI continues to be associated with adverse outcomes, including high mortality and partial renal recovery.*

Keywords: *Acute Kidney Injury, PICU children, AKIN staging*

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I. Introduction

Acute Kidney Injury (AKI), erstwhile known as Acute Renal Failure (ARF) is a clinical syndrome appertaining to a reversible accumulation of urea, Creatinine and nitrogenous waste products and disturbances in maintenance of fluid and electrolyte homeostasis[(1)]. Acute kidney injury (AKI) is a common co-morbidity in critically ill children and is associated with an increased risk of morbidity and mortality[(2)]. There is a wide variation in reported incidence of AKI ranging from 10%-80%[(3)] due to varied definitions of AKI.

A uniform definition for acute kidney injury (as mentioned in table 1) has existed only since 2004, when the Acute Dialysis Quality Initiative (ADQI) proposed the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria[(4)] for AKI in adults. Later in 2007, a modified paediatric RIFLE (p-RIFLE)[(5)] emerged. Since then two modifications of the RIFLE: Acute Kidney Injury Network (AKIN) (2007)[(6)], and Kidney Disease: Improving Global Outcomes (KDIGO) (2012)[(7)] have emerged. All of the three modern definitions are based on changes in serum or plasma creatinine (Cr) and urine output (UO).

In view of the limited data available on the incidence and clinical profile of pediatric AKI from Indian children, and the regional variations in the clinical profile of AKI, the present prospective study was conducted in Institute of Child Health & Research Centre, Madurai Medical College, Madurai.

Table 1: Current Criteria used for diagnosis of Acute Kidney injury

Classification	Stage	Creatinine criteria	Urine output criteria
RIFLE (Bellomo et al., 2004)	Risk	Increased creatinine x1.5 or GFR decrease >25%	<0.5 ml/kg/h x 6h
	Injury	Increased creatinine x2 or GFR decrease >50%	<0.5 ml/kg/h x 12h
	Failure	Increased creatinine x3 or GFR decrease >75% or creatinine ≥4 mg/100ml (acute rise of ≥0.5 mg/100ml dl)	<0.3 ml/kg/h x 24h or anuria x 12h
	Loss	Persistent ARF = complete loss of renal function > 4 weeks (defined as the need for renal replacement therapy (RRT) for >4 weeks)	
	End-stage	End-stage renal disease (defined as the need for dialysis for >3 months)	

Pediatric RIFLE (pRIFLE) (Akcan-Arikan et al., 2007)	Risk Injury Failure Loss End-stage	eCCl decrease by 25% eCCl decrease by 50% eCCl decrease by 75% or eCCl <35 ml/min/1.73m^2 Persistent failure >4 weeks End-stage renal disease (persistent failure >3 months)	<0.5 ml/kg/h x 8h <0.5 ml/kg/h x 16h <0.3 ml/kg/h x 24h or anuria x 12h
AKIN (R. L. Mehta et al., 2007)	1 2 3	Increased creatinine x 1.5-2 or creatinine increase ≥0.3 mg/dl Increased creatinine x 2-3 Increased creatinine x ≥3 or creatinine ≥4.0 mg/dl with an acute increase of 0.5 mg/dl	<0.5 ml/kg/h x 6h <0.5 ml/kg/h x 12h <0.3 ml/kg/h x 24h or anuria x 12h
KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012)	1 2 3	Increased creatinine x1.5-1.9 or ≥0.3 mg/dl increase Increased creatinine x2.0-2.9 Increased creatinine x3 or creatinine ≥4.0 mg/dl or initiation of RRT or eGFR <35 ml/min per 1.73m^2 (<18 years)	<0.5 ml/kg/h x 6-12h <0.5 ml/kg/h x ≥12h <0.3 ml/kg/h x ≥24h or anuria x ≥12h

AKIN: Acute Kidney Injury Network; GFR: glomerular filtration rate; eCCl: estimated creatinine clearance; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; RRT: renal replacement therapy

II. Aim Of The Study

To determine the incidence, clinical profile, outcome and predictors of mortality of Acute Kidney Injury using AKIN staging in critically ill children admitted in Paediatric Intensive Care Unit of a Tertiary Care Hospital.

III. Methodology

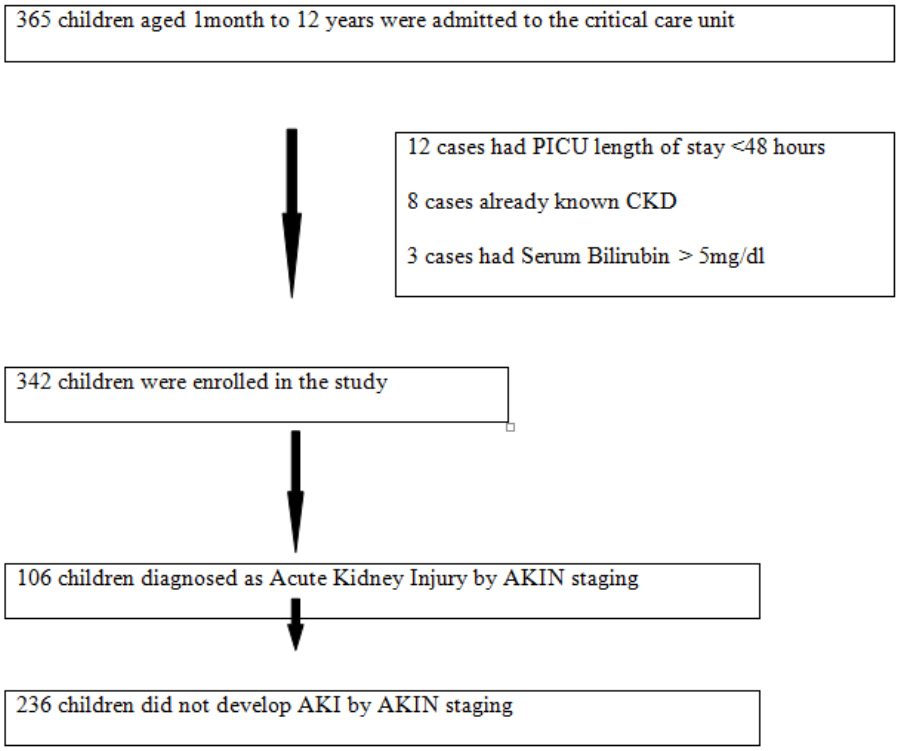
The design is a prospective observational study of critically ill children admitted to Paediatric Intensive care Unit (PICU) at Institute of Child Health and Research Centre, Govt. Rajaji Hospital, Madurai.

- All children within the age group of 1 month to 12 years with length of stay for atleast 48 hours in PICU over a period of 1 year (July 2015 – June 2016) were included in the study after getting consent from parents.
- PICU admission was based on one or more of the following criteria[8]:
  - Impaired level of consciousness (Glasgow coma scale < 8)
  - Signs suggestive of severe increase in intracranial pressure (e.g., hypertension, bradycardia, papilledema)
  - Hypoventilation or respiratory failure (oxygen saturation < 90% or arterial oxygen (PaO_2) <60 mmHg with supplemental oxygen or arterial CO_2 ($PaCO_2$) >60 mmHg)
  - Uncontrollable or poorly controlled seizures
  - Hypotension requiring inotropic support
  - Requirement of renal replacement therapy (RRT)
  - Fulminant hepatic failure.
- EXCLUSION CRITERIA
  - Patients with known chronic kidney disease
  - Bilirubin level >5 mg/dl
  - PICU stay less than 48 hours
- Institutional ethical committee approval obtained

Following informed parental consent, information regarding the diagnosis, co morbidities and the serial serum creatinine levels were recorded. For all the children serum creatinine levels were done within 48hrs of illness and then repeated every consecutive day. The data collected regarding all the selected cases were entered in Microsoft excel sheet 2010. Results were analyzed using the SPSS version 19 (IBM corporation, New York, U.S.A). Continuous data were reported as mean ± SD (if normally distributed) and median (range) (if non-normally distributed). Categorical variables were expressed as proportions. Continuous variables with normal distribution were compared using Student *t*-test while those not normally distributed were analyzed using Mann Whitney U test. Categorical data were analyzed using Pearson Chi-square test or Fischer exact test. P value was calculated using chi square test.

IV. Results

Our study enrolled 342 children in the time period of 12 months and observed for the development of Acute Kidney Injury.



On the whole, 342 critically ill children admitted to PICU were screened for AKI. 106 children developed AKI giving an incidence of 31%. Of the children enrolled in our study, 198 (57.9%) were male and 144 (42.1%) were female. Of the 106 children who developed AKI, 58 (54.7%) were male and 48 (45.3%) were female.

The severity of Acute Kidney Injury was given by the staging of Acute Kidney Injury. According to AKIN staging, stage 1 included 43 (40.6%) cases, stage 2 included 28 (26.4%) cases, stage 3 included 35 (33%) cases as shown in table 2.

TABLE 2: CASE DISTRIBUTION

STAGING	CASES
STAGE 1	43 (40.6%)
STAGE 2	28 (26.4%)
STAGE 3	35 (33%)
TOTAL	106 (100%) (P Value <0.0001)

Median age of the entire study population was 30 months (range 2 - 144 months). Median age of children with AKI was 36 months (range 2 - 144 months). Median age of children who succumbed with AKI was 24 months (range 2 – 144) and the median age of children who survived was 42 months (range 2- 144).

Mean duration of stay among the children who developed AKI (n=106) was 9.4 ± 4.5 days whereas the Mean duration of stay among the children who did not develop AKI was 5.6 ± 3.2 days. Mean duration of stay who survived with AKI was 11.1 ± 4.1 days while the mean duration of those who died was 7.1 ± 4.0 days.

The etiological factors of Acute Kidney Injury are listed in Table 3. Infections constitute 56.6% cases (60/106) of AKI. Sepsis was made as diagnosis in 18 cases of which 15 were culture positive and 3 were culture negative. Organisms isolated includes Coagulase Negative Staphylococcus (6 children), Staphylococcus aureus (3 children), Non fermentative gram negative bacillus (3 children), Klebsiella pneumonia (2 children), E. coli (1 child). Other common etiologies were Meningoencephalitis, Urinary Tract Infections (UTI), Congenital heart diseases, Snake envenomation, Scorpion sting, Acute Glomerulonephritis, HUS d+, Nephrotic syndrome and surgical causes. Of the 7 cases of UTI, organisms isolated include profuse growth of E.coli (4 cases), profuse growth of Coagulase Negative Staphylococcus (2 cases), Non fermentative gram negative bacillus (1 case).

Mortality rate in children with AKI (as described by AKIN stage) was found to be 42.5% in our study. 45 out of 106 expired during the study. Among the AKIN stage I cases 15/43 (34.9%) died, in stage II cases 11/28 (39.3%) died and in stage III cases 19/35 (54.3%) died as shown in table 4.

Mortality were highest in the Bronchopneumonia and Meningoencephalitis group. 81.8% (9/11 cases) died among Bronchopneumonia and 68.6% (11/16 cases) died among Meningoencephalitis, 55.6% (10/18 cases) died among sepsis cases. No mortality among scorpion sting, nephrotic syndrome cases. The mortality in children < 10 months of age was found to be high as compared with age group of >10 months and this difference was statistically significant (p value 0.0406).

A total of 49 children of the survivors with AKI (80.3%) had complete renal recovery while 12 children (19.7%) of the survivors had partial renal recovery. 12 children who had partial renal recovery at the time of discharge were followed up over a period. Among the 12, 4 had hypertension and 8 had elevated creatinine levels.

In AKI stage 1, out of the survivors, 27 (96.4%) had complete renal recovery while 1 (3.6%) had partial renal recovery at discharge. In AKI stage 2, 13 (76.5%) had complete renal recovery while 4 (23.5%) had partial renal recovery at discharge. In AKI stage 3, 9 (56.3%) had complete renal recovery, while 7 (43.7%) had partial renal recovery at discharge as shown in table 5.

TABLE 3: ETIOLOGICAL PROFILE OF ACUTE KIDNEY INJURY

ETIOLOGY	**N (%)**
Infections	**60 (56.6%)**
Cardiac causes (Congenital heart disease and Congestive Cardiac Failure)	9 (8.5%)
Snake envenomation	7 (6.6%)
Status Epilepticus (Seizure disorder, Febrile Seizures, Toxin induced)	5 (4.7%)
Surgical causes (PUJ obstruction, Hydroureteronephrosis, Hypoplastic kidney, Ewings sarcoma)	5 (4.7%)
Acute Glomerulonephritis	4 (3.8%)
Scorpion sting	4 (3.8%)
HUS d+	3 (2.8%)
Nephrotic syndrome	3 (2.8%)
Poisoning (Organophosphorus, Abrus precatorius, Native Medication)	3 (2.8%)
Diabetic Ketoacidosis	2 (1.9%)
Acute severe asthma	1 (0.9%)
AMONG INFECTIONS (N=60)	
Sepsis ● Culture positive ● Culture negative	18 (30%) 15 (83.3%) 3 (16.7%)
Meningoencephalitis	16 (26.7%)
Bronchopneumonia	11 (18.3%)
Urinary Tract Infection	7 (11.7%)
Viral hemorrhagic fever	5 (8.3%)
Acute watery diarrhea	2 (3.3%)
Empyema thorax	1 (1.7%)

TABLE 4: MORTALITY AMONG AKI CASES

AKIN STAGE	**SURVIVORS**	**DEATH**	**TOTAL**
STAGE 1	28 (65.1%)	15 (34.9%)	43 (100%)
STAGE 2	17 (60.7%)	11 (39.3%)	28 (100%)
STAGE3	16 (45.7%)	19 (54.3%)	35 (100%)
TOTAL	61 (57.5%)	45 (42.5%)	106 (100%)

TABLE 5: SHORT TERM OUTCOME

	STAGE 1	**STAGE 2**	**STAGE 3**	**TOTAL**
COMPLETE RENAL RECOVERY	27 (96.4%)	13 (76.5%)	9 (56.3%)	49 (80.3%)
PARTIAL RENAL RECOVERY	1 (3.6%)	4 (23.5%)	7 (43.7%)	12 (19.7%)
TOTAL	28 (45.9%)	17 (27.9%)	16 (26.2%)	61 (100%)

A total of 28 children (26.4%) required dialysis in the form of peritoneal dialysis. The mortality among children requiring RRT was similar to children not requiring RRT (42.9% vs. 42.3%) and the difference was not significant statistically. Requirement of RRT was not related to age or the etiology of AKI.

Hyponatremia (57.5%), Hypernatremia (16%), hypokalemia (22.6%), hyperkalemia (18.9%), anemia (55.7%), thrombocytopenia (23.6%), hypertension (15.1%) and metabolic acidosis (57.5%) were the associated complications and co-morbidities found in children with acute kidney injury in our study.

A total of 59 children (55.7%) out of 106 AKI children needed mechanical ventilation and 77 children (72.6%) had shock as co-morbidity. Table 6 compares variables between survivors and non survivors with Acute Kidney Injury.

TABLE 6: Comparison of survivors and deaths in critically ill children with AKI

Parameter	**Survivors (n=61)**	**Deaths (n=45)**	**P value**
Age (months) [median(range)]	42 (2-144)	24 (2-144)	0.02
Sex [N (%)]	Male – 31 Female – 30	Male -27 Female - 18	0.348
Duration of stay (days) (mean±SD)	11.1 ± 4.1	7.1 ± 4.0	0.001
Mechanical ventilation [N (%)]	19 (31.1%)	40 (88.9%)	0.0001
Shock [N (%)]	35 (57.4%)	42 (93.3%)	0.0001
Renal Replacement Therapy [N (%)]	16 (26.2%)	12 (26.7%)	0.960
Maximum creatinine value (mean±SD)	1.9 ± 1.4	2.4 ± 2.1	-
Morbidities [N (%)]			
Bronchopneumonia	2 (18.2%)	9 (81.8%)	
Meningoencephalitis	5 (31.3%)	11 (68.7%)	
Sepsis	8 (44.4%)	10 (55.6%)	
AGN	3 (75%)	1 (25%)	
Snake envenomation	6 (85.7%)	1 (14.3%)	
Scorpion sting	4 (100%)	0	
Nephrotic syndrome	3 (100%)	0	

The predictors of mortality on univariate analysis were: Age less than 10 months, shock and requirement of mechanical ventilation, presence of metabolic acidosis as shown in table. In the multivariate model, requirement of mechanical ventilation was found to be an independent predictor of mortality. (odds ratio: 15.011; 95% Confidence Interval 3.086-73.008; P value 0.001) shown in table 7.

TABLE 7: Predictors of mortality in Acute Kidney Injury (Univariate analysis)

PARAMETER	**DEATH**	**SURVI-VORS**	**ODDS RATIO**	**95% CI**	**P value**
Age					
<10 months	**16**	**11**	**2.51**	**0.94-6.75**	**0.0406#**
>10 months	**29**	**50**			
Gender					
Male	**27**	**31**	**1.45**	**0.68-3.41**	**0.347**
Female	**18**	**30**			
Stage of AKI					
Stage 1	**15**	**28**	**0.59**	**0.24-1.41**	**0.192**
Stage 2	**11**	**17**	**0.84**	**0.32-2.20**	**0.692**
Stage 3	**19**	**16**	**2.06**	**0.84-5.08**	**0.083**
Oliguria	**19**	**21**	**1.39**	**0.58-3.32**	**0.413**
Metabolic acidosis	**33**	**28**	**3.24**	**1.31-8.13**	**0.004#**
Hyponatremia	**25**	**36**	**0.87**	**0.37-2.03**	**0.721**
Hypernatremia	**9**	**8**	**1.66**	**0.52-5.29**	**0.339**
Hyperkalemia	**9**	**11**	**1.14**	**0.38-3.35**	**0.798**
Hypertension	**4**	**12**	**0.40**	**0.10-1.48**	**0.125**
Mechanical ventilation	**40**	**19**	**17.68**	**5.50-60.79**	**0.0001#**
Anemia	**28**	**31**	**1.59**	**0.68-3.77**	**0.242**
Thrombocytopenia	**10**	**15**	**0.88**	**0.32-2.39**	**0.776**
Requirement of RRT	**12**	**16**	**1.02**	**0.39-2.67**	**0.959**
Shock	**42**	**35**	**10.4**	**2.9-37.3**	**0.0001#**

#P value significant, RRT: Renal Replacement Therapy, CI: Confidence interval, AKI: Acute Kidney Injury

V. Discussion

From our observational study, the incidence of Acute Kidney Injury in critically ill children admitted to PICU in our institute was found to be 31% using AKIN staging. The incidence in this study was comparable with a study done by Sriram krishnamurty et al at JIPMER[8], where the incidence was reported to be 25.1% in PICU and by Mehta P et al at AIIMS[9], where the incidence was 36.1%.

Assessing the severity of AKI is useful in predicting mortality rates and the need for renal replacement therapy. In the present study as AKIN criteria was used for the classification of AKI, which might have lead to a relatively higher incidence of AKI stage I.

In our study, the most common cause of Acute Kidney Injury was infections (56.6%). Of which, sepsis constitutes 30% (overall 17%). Other common etiologies being meningoencephalitis (15.1%), bronchopneumonia (10.4%), cardiac causes (8.5%), UTI (6.6%), snake envenomation (6.6%), viral hemorrhagic fever and status epilepticus constitute 4.7% each, AGN (3.8%), scorpion sting (3.8%), HUS d+ (2.8%), nephritic syndrome (2.8%). Previous studies show sepsis, glomerulonephritis and HUS as predominant etiologies in developing countries, which have been replaced by hemato-oncological complications and pulmonary failure as causes of AKI in west[8,10]. Increased risk of developing AKI has been mentioned with pneumonia, but seems to have been under-reported in children[11]. In a study by Garuda Rama et al[12], the most common associated etiology with AKI was sepsis. 7 cases of snake envenomation and 4 cases of scorpion sting were reported in our study to be associated with AKI which is a common problem in some parts of India[13]. The mortality in AKI in children also has been reported to vary widely from 16% to 43.8%[8,10,14,15]. In our study, it was 42.5% by AKIN staging, which is comparable to a recent study from Kuwait reporting 43.8% mortality[14]. The mortality rate in a study by Sriram Krishnamurthy et al[8] was found to be 46.3%. In the study by Shweta naik et al[16], mortality was found to be 15.5% in AKI group. In a study by Mehta et al[9], the mortality was 37% in AKI group.

Apart from mortality, the other short term outcomes that were observed in our study were the complete and partial renal recovery. A total of 49 children of the survivors with AKI (80.3%) had complete renal recovery while 12 children (19.7%) of the survivors had partial renal recovery at discharge. Majority of partial renal recovery belong to stage 3, indicating towards significant morbidity associated with Acute Kidney Injury. This observation was comparable with the study by Sriram Krishnamurthy et al[8], where 20.7% children who survived with AKI had partial renal recovery at the time of discharge. In a study by Shweta naik et al[16], 38.8% children had partial renal recovery.

In our study, the predictors of mortality on univariate analysis were: Age less than 10 months, shock and requirement of mechanical ventilation, presence of metabolic acidosis. In the multivariate model, requirement of mechanical ventilation was found to be an independent predictor of mortality.

VI. Conclusion

This article has added to the literature regarding the incidence of acute kidney injury in critically ill children and helps to highlight on the importance and scope of AKI in this patient population. The incidence of Acute Kidney Injury among critically ill children admitted to ICH&RC, Madurai was 31%. The mortality rate was 42.5% in critically ill children and 19.7% patients with AKI had partial renal recovery at the time of discharge. 26.4% patients required Renal replacement therapy. One consideration to be made in relation to surviving patients is that they have a high risk of long-term renal complications. Thus further studies with multicenter trails and multivariate analysis were required for early detection of AKI and early intervention in order to decrease the mortality and morbidity due to acute kidney injury.

LIMITATIONS

Some of our study limitations were

- It was a single centre observational study. Therefore only associations can be shown, and no absolute causality.
- Being a tertiary care centre, we receive a lot of referral cases from peripheral hospitals. Lack of pre-referral treatment documentation concerning intravenous fluids, nephrotoxins like non-steroidal anti-inflammatory drugs, gentamycin which could have changed the initial presentation.
- Diet, as a major factor influencing serum creatinine was not considered in this study.

DECLARATIONS

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Conflict of interest: Nil
Ethical approval: Cleared

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