Clinical profile and outcome of acute kidney injury in children admitted to paediatric intensive care unit: A prospective observational study

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Abstract

Introduction: Acute kidney injury (AKI) is a commonly encountered problem in the paediatric intensive care unit (PICU). There are limited reports on paediatric AKI from the Indian subcontinent.

Objective: To determine the incidence, aetiology and outcome in paediatric AKI using Acute Kidney Injury Network (AKIN) criteria.

Method: This prospective observational study was conducted in the PICU of a teaching hospital in Western Maharashtra, India, from July 2016 to June 2017 on patients aged 1 month to 17 years.

Results: The incidence of AKI was 18.8% (80/426). The mean age was 70 \pm 60 months. Most (66.3%) cases had stage I AKI and 54% developed AKI within 72 hours. Sepsis (35%), pneumonia (25%) and tropical febrile illnesses (18.7%) were the common aetiologies. Complete recovery (CR) was seen in 79% and partial recovery (PR) in 21%. CR was highest in stage I (91%) as compared to stages II and III (p=0.005). Mortality was 22% (18/80). Mortality significantly increased with the stage of AKI (p=0.003). Mechanical ventilation, inotrope support, shock and the stage of AKI had a significant association with mortality on bivariate analysis. Mechanical ventilation was found to be a significant independent predictor of mortality (p= 0.011). Renal replacement therapy was needed in 6 (8%) cases.

Conclusions: About one-fifth of children admitted to ICU developed AKI and most experienced mild transient AKI. Moderate to severe AKI carried high mortality suggesting a dose-response effect. Infections remain the commonest cause and mechanical ventilation was an independent predictor of mortality.

(Key words: Acute kidney injury, AKIN criteria, Sepsis, PICU, Predictors of mortality)

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Introduction

Acute kidney injury (AKI) is a common complication in critically ill children associated with significant morbidity and mortality. Recent hospital studies have reported an incidence varying from 15-36% in critically ill children^{1,2,3}. Different classifications used for paediatric AKI include paediatric Risk, Injury, Failure, Loss, Endstage-renal disease (p-RIFLE) classification, Acute Kidney Injury Network (AKIN) classification and Kidney Disease Improving Global Outcomes (KDIGO) classification.

A comparative study using the above classifications found that although the use of different classifications resulted in differences in incidence and staging, all three had a similar association with morbidity and mortality⁴. Serum creatinine is an imperfect marker of kidney injury. Moreover, serum creatinine rises only after 25-50% of kidney function is lost and up to 72 hours after the insult⁵. Measuring urine output in infants and young children has inherent difficulties. The Assessment of Worldwide Acute-kidney-injury, Renal-angina and Epidemiology (AWARE) study demonstrated that serum creatinine alone failed to identify AKI in 67.2% of patients with low urine output⁶. This reinforces the need for accurate measurement of urine output in critically ill or at-risk children for active surveillance of AKI.

Various studies have shown that AKI is an independent risk factor for prolonged intensive care unit (ICU) stay, longer duration of mechanical ventilation and increased mortality in children^{6,7}. The mortality in AKI has been reported to vary from 16 to 43%^{8,9,10}. AKI is also a common but frequently missed complication in children admitted to wards, especially in those receiving nephrotoxic drugs. The mortality is three-fold higher in critically ill children compared to non-critical children¹¹. While in developed countries the aetiology has shifted from primary glomerular disorders to hospital-acquired AKI, factors like dehydration, sepsis and haemolytic uraemic syndrome remain common in developing countries¹².

The patients from developing countries tend to be younger and infections account for most of the causes¹³. The management of AKI may also vary from one centre to another depending on the level of expertise and resources available. The exact incidence of AKI in Indian paediatric intensive care unit (PICU) is not known as there are only limited single-centre reports from India. Nevertheless, understanding the regional differences in the incidence and aetiology will help identify high-risk children as prevention is the guiding principle in the management.

Objectives

The present study was undertaken to determine the incidence, clinical profile and outcome of AKI in critically

ill children using Acute Kidney Injury Network (AKIN) criteria.

Method

This prospective observational study was conducted in the PICU of a teaching hospital in Western Maharashtra, India, from July 2016 to June 2017.

Inclusion and exclusion criteria: All patients aged 1 month to 17 years admitted to the PICU during the study period were assessed for eligibility. Patients with chronic kidney disease, those on diuretics, whose serum bilirubin level \geq 5mg/dl and those with PICU stay less than 48 hours / discharged against medical advice, were excluded.

Sample size: The sample size was calculated using the statistical formula, based on the prevalence (25.1%) from an earlier Indian study by Krishnamurthy¹⁰.

Detailed history, examination and relevant investigations were done as per existing protocol. Paediatric Risk of Mortality III (PRISM III) score was done in all subjects within 24 hours of admission.

Either serum creatinine or urine output criteria were used to diagnose and stage AKI. Serum creatinine was done in all patients at admission (initial) and then every 24 hours to check for AKI. In those who developed AKI, creatinine was repeated every 24 hours till it normalized. Urine output was measured every 6 hours. Staging of AKI was done as per AKIN criteria². If there was a subsequent rise in serum creatinine values during PICU stay, AKI was restaged accordingly. Serum creatinine estimation was performed by the modified Jaffe method using the autoanalyser.

The reference range of serum creatinine was taken as follows: 1 month to 1 year 0.2-0.4mg/dl,1 year to 12 years 0.3-0.7mg/dl,12 years to 17 years 0.8-1.0mg/dl^{14,15}.

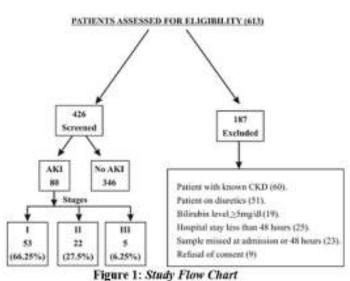
The outcome was recorded in terms of complete or partial recovery and mortality. Need for mechanical ventilation, inotrope support, renal replacement therapy and duration of PICU stay were noted. Complete recovery (CR) was defined as normal serum creatinine for age, normal urinalysis and blood pressure at discharge. Partial recovery (PR) was considered when there was decrease in serum creatinine but still elevated for the age or persistent hypertension or abnormal urinalysis at discharge. The incidence of AKI was defined as its occurrence as a proportion of total admissions

Ethical issues: The study was approved by the Institutional Ethics Committee of Bharati Vidyapeeth Deemed University Medical College and Hospital, Sangli, Maharashtra, India (No. BVDUMC&H/ Sangli/ IEC/ Dissertation 2015-16/ 125) on 8.12.2015. Informed written consent and assent wherever applicable were obtained before the inclusion of subjects into the study.

Statistical analysis: The categorical variables were summarized as frequencies and percentages. The quantitative variables were presented as mean and standard deviation. An unpaired t-test and Chi-square test were applied to check the difference in means of the variables and proportions or association between survivors and non-survivors respectively. Binary logistic regression was used to fit the regression model for outcomes - survivors and non-survivors. Statistical analysis of the result was done using Microsoft Office 365 and SPSS version 22 software. (IBM Corp, Armonk, New York, USA)

Results

The flow of study participants is depicted in Figure 1.



Out of 426 patients screened 80 (18.8%) developed AKI. There were 53 (65.4%) males and 27 (33.3%) females. Mean age was 70 ± 60 months. Age-wise, 26 (32.5%) were under 12 months of age, 18 (22.5%) were between 13 months to 5 years and 36 (45%) between 6 to 17 years. PRISM score at admission was <20 in 63 (78%) and \geq 20 in 17 (22%) cases; 43 (54%) patients developed AKI within 72 hours, 25 (31%) within 7 days and 12 (15%) after 7 days of PICU admission. General characteristics of study subjects are shown in Table 1.

Table 1: General characteristics (n=80)				
Variable	Result			
Stages of acute kidney injury (AKI): n (%)				
Ι	56 (70.0)			
II	19 (23.8)			
III	05 (06.3)			
PRISM score: Mean \pm SD	5.59 ± 6.15			
Admission to the onset of AKI (days): Mean \pm SD	5 ± 3			
Time for resolution of AKI	3 ± 2			
Paediatric intensive care unit stay (days): Mean $\pm SD$	5.8 ± 3.56			
<i>Complete recovery:</i> n (%)	49 (61.3)			
Partial recovery: n (%)	13 (16.3)			
Mortality: n (%)	18 (22.5)			
Mechanical ventilation: n (%)	26 (32.5)			
Inotrope support: n (%)	39 (48.8)			
<i>Renal replacement therapy:</i> n (%)	07 (08.9)			
The maximum value of serum creatinine (mg/dL): Mean \pm SD	1.45 ± 0.67			

Sepsis (35%) was the most common aetiological factor followed by pneumonia (25%) and tropical febrile illness (18.8%). While dengue was the commonest tropical infection, others included scrub typhus, malaria and enteric fever (Table 2). Urinary tract infection, nephrotic

syndrome, glomerular nephritis and renal vein thrombosis constituted the renal aetiologies. Miscellaneous causes included juvenile myasthenia gravis, diabetic ketoacidosis, acute lymphocytic leukaemia and haemophagocytic lympho-histiocytosis.

Table 2: Aetiology of acute kidney injury according to the primary diagnosis

Diagnosis	Number of patients (%)		
Sepsis	28 (35.0)		
Pneumonia	20 (25.0)		
Tropical febrile illness	15 (18.8)		
Dengue	11 (13.8)		
*Others	04 (05.0)		
Acute diarrhoeal disease	08 (10.0)		
Renal	07 (08.9)		
Acute central nervous system infection	04 (05.0)		
Poisoning	03 (03.8)		
Miscellaneous	07 (08.8)		

*Others: Enteric fever, scrub typhus, malaria

Complete recovery was highest in stage I (91%) compared to stage II (43%) and stage III (50%) (p = 0.005). Partial recovery was seen in 9% (4/46) in stage I; 56% of survivors in stages I and II had only PR. In stage I, among the 42 survivors, 28 (67%) had CR in 3 days, 11 (26 %) in 4-7 days and 3 (7%) in 8-12 days. In stages II and III, out of 7 with CR, 1 (14%) had CR in 3 days, 3 (42%) in 4-6 days and 3 (42%) in 7-12 days (p = 0.035).

Overall, 59% of subjects had CR in 3 days. Mean duration for CR was 3±21 days. Out of 80 cases, 18 (22%) died. Mortality was 13% (7/ 53) in stage I, 36% (8/22) in stage II and 60% (3/5) in stage III (p = 0.003).

Stage of AKI, mechanical ventilation, inotrope support and shock had a significant association with mortality on bivariate analysis (Table 3).

Parameter	Survivors (n=62)	Non-survivors (n=18)	Significance	
Age (months): Mean \pm SD	73.52 ± 62.85	59.28 ± 47.68	p = 0.309	
Sex: n (%)				
Male	44 (70.0)	09 (50.0)	p = 0.091	
Female	18 (30.0)	09 (50.0)		
PRISM score: Mean \pm SD	5.47 ± 6.33	6.35 ± 5.56	p = 0.577	
Stage of acute kidney injury: n (%)				
Ι	49 (79.0)	07 (38.9)		
II	11 (17.7)	08 (44.4)	p = 0.003	
III	02 (03.2)	03 (16.7)	_	
<i>Time of onset of AKI (days): Mean</i> \pm <i>SD</i>	3.7 ± 2	4.6 ± 3.5	p = 0.208	
Shock: n (%)	30 (48.0)	15 (83.0)	p = 0.006	
Inotrope support: n (%)	25 (40.3)	14 (77.8)	p = 0.005	
Mechanical ventilation: n (%)	12 (19.4)	14 (77.8)	p = 0.000	
Renal replacement therapy: n (%)	05 (08.1)	02 (11.1)	p = 0.687	
Maximum serum creatinine (mg/dl) : Mean \pm SD	1.4 ± 0.63	1.65 ± 0.78	p = 0.232	

Table 3: Compariso	of clinical	parameters between	survivors and	l non-survivors
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p < 0.05 - significant

The binary logistic regression model was statistically significant and correctly classified 86.3% of cases. Mechanical ventilation was found to be a significant

predictor and those who were ventilated had a 9.99 times higher risk of mortality (Table 4).

Variables in the	В	S.E.	Wald	Df	Sig.	Odds	ds 95% CI for Odd	
equation						ratio	Lower	Upper
AKI stage			4.211	2	0.122			
AKI stage I	2.063	1.215	2.881	1	0.09	7.866	0.727	85.139
AKI stage II	0.967	1.272	0.578	1	0.447	2.629	0.217	31.775
Inotrope support	0.228	0.937	0.059	1	0.808	1.256	0.2	7.881
Mechanical ventilation	2.302	0.734	9.824	1	0.002	9.989	2.369	42.128
Shock	0.324	0.826	0.154	1	0.694	1.383	0.274	6.977
Constant	-1.797	1.277	1.979	1	0.16	0.166		

 Table 4: The overall percentage of the model for correctness - 86.3%

B: Regression coefficient, S.E.: Standard Error, Wald: Wald's Coefficient, df: degrees of freedom, Sig.: Significance

Renal replacement therapy (RRT) was needed in 6 (8%) cases of stage II and stage III AKI (3 peritoneal dialysis and 3 haemodialysis). Other coexisting conditions were anaemia in 52 (65%) shock in 45 (56.3%), metabolic acidosis in 31 (38.8%) and thrombocytopenia in 28 (35%) cases.

Discussion

The incidence of AKI in the present study was 18.7%. Our finding is comparable with other Indian studies which reported an incidence of 20%-25% using AKIN criteria^{10,16,17}. A study from Bangladesh which included newborns to 17 years reported a high incidence of 61%⁹. The first multinational prospective study on paediatric AKI, AWARE conducted on 4683 children showed a prevalence of 26.9% and severe AKI in 11.6% using KDIGO definition⁶. A recent meta-analysis which included studies using KDIGO 2012 criteria reported an overall incidence of 26% and 14% in moderate and severe AKI¹⁸. The heterogeneity of the study population, study design, definitions used and regional differences may explain this wide variation.

The mean age of subjects was 70±60 months with male preponderance (66%). Infants constituted 32.5% of the study. AKI is reported to be commoner in young males^{9,19,20}. The aetiology of AKI can be broadly classified as hospital-acquired and community-acquired¹⁹. The causes in developed countries include haemorrhage, infections and septic shock²¹. In contrast, causes encountered in developing countries include infections like pneumonia, diarrhoea, sepsis, tropical fevers and acute glomerular diseases.

Sepsis (35%) was the most common aetiological factor in the study followed by pneumonia (25%) and tropical febrile illness (18.8%). Dengue (11/15) constituted the majority of tropical infections. Sepsis as the commonest cause has been reported by many authors from developing countries^{20,22,23}. AKI is a frequent complication of community-acquired pneumonia (CAP) in children. Our finding is comparable to an earlier study which reported AKI in 20% of hospitalized children with CAP. Severe pneumonia, high C-reactive protein values and longer duration of symptoms were independent predictors for AKI²⁴. In tropical countries, a significant proportion of AKI follows illnesses like dengue, scrub typhus, malaria and leptospirosis as was the case in our study. Tropical infections accounted for 9% to 30% of various Indian studies^{10,19}. Thus infections remain the main cause of AKI.

Forty-three (54 %) cases developed AKI within 72 hours and 85% within 7 days of admission. AKI generally occurs early in the course of ICU stay or many times it is already present at admission^{6,25}. The AWARE study concluded that AKI occurred during the first 7 days after ICU admission⁶. The time of onset of AKI and its impact on outcome has not been well studied. An attempt to categorize AKI into different phenotypes based on the time of onset and resolution was done in a secondary analysis of the AWARE database. They defined transient AKI as creatinine normalizing within 48 hours. Those without recovery were classified as persistent. Patients were subsequently grouped into distinct phenotypes like early-transient, early persistent, late-transient, late persistent and recurrent²⁶. They found that the time of resolution of AKI was a significant predictor and early persistent AKI had a strong association with poor outcome. Most of our subjects had early transient AKI with relatively good outcomes. Early stages of AKI may be missed allowing progression to an irreversible stage. Hence, close monitoring of high-risk patients, reduction of additional risk factors and optimization of fluid status and blood pressure are critically important.

The majority (66%) of our patients had stage I disease. Similar observations were reported by other studies^{6,17}. However, studies from Iran and Bangladesh reported the highest number of patients in stage III^{9,27}. Among survivors, CR was seen in 79% and PR in 21%. Our results are comparable to other authors^{10,28}. The mean duration taken for CR in survivors was 3 ± 2 days. The majority (91%) of patients with stage I AKI had CR whereas only 43% in stage II and 50% in stage III had CR and this was statistically significant. RRT was required in six patients with stage II and III disease. Time taken for CR was significantly more in moderate to severe AKI as compared to mild AKI (p=0.035)

The mortality was 22.5% in the present study. Our result is comparable to other Indian studies^{8.10.25}. As expected, there was an incremental rise in mortality with higher stages. Mortality was 13% in stage I, 36% in stage II and 60% in stage III (p= 0.003). Similar observations were reported by other authors⁶. A recent meta-analysis, which included 94 studies from 26 countries, reported the overall mortality was 11% with higher mortality of 18-22% in low and middle-income countries. They concluded that although the burden of AKI was similar, the mortality was higher in middle and low-income countries¹⁸.

In our study, stage of AKI, mechanical ventilation, shock and inotrope support had significant associations with mortality on bivariate analysis. However, on binary regression analysis, only mechanical ventilation (multivariate p = 0.011) was found to be an independent predictor of mortality. Mechanical ventilation as an independent predictor has been reported by earlier authors^{9,17,29}.

There were some limitations. Being a single-centre study, we cannot generalize our findings to other ICU settings and we did not compare outcomes between AKI and non-AKI cohorts.

Conclusions

About one-fifth of children admitted to ICU developed AKI and most experienced early transient AKI. Moderate to severe AKI carried high mortality, suggesting a doseresponse effect. Infections remain the commonest cause of AKI and mechanical ventilation was an independent predictor of mortality.

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