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Incidence of Acute Kidney Injury and Determinant Factors in Children Admitted to a Tertiary Hospital

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Abstract: *acute kidney injury is common in hospitalized children and this study characterizes acute kidney injury in hospitalized children in a tertiary care center. Identify the incidence and risk factors of acute kidney injury in hospitalized children. The study is prospective, institution based and observational. During the study period, 5348 children were admitted among which 68 children developed AKI with an incidence rate of 12.7/1000 admissions. Severe AKI was 64.7%. The mortality rate with AKI was 26.5% when compared with 8.7% without AKI. Age 5-14 years had a 1.2 times higher risk of developing AKI than children under five years (adjusted HR 1.22; 95% CI, 0.74-2.98). Females had 2.8 times higher risk of developing AKI (adjusted HR 2.79; 95% CI, 1.29-6.02) than males. Children with heart failure, malignant diseases and sepsis had 3.7, 4.5 and 8.0 times higher risk of developing AKI than other diagnosis respectively with (AHR 3.74; 95% CI, 1.34-10.4), (AHR 4.50; 95% CI, 1.78-11.4) and (AHR 8.09, 95% CI, 1.88-34.8) respectively. Children with severe AKI had the highest mortality AHR 2.68, 95% CI (0.96, 7.47) when compared with non-severe AKI AHR 0.85, 95% CI (0.20, 3.56). AKI is common in hospitalized children and it is a significant cause of mortality.*
Keywords*: acute kidney injury, AKIN, Ethiopia*

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I. Introduction

Acute kidney injury (AKI) is a syndrome with a sudden deterioration of the function of the kidneys and it is commonly seen in hospitalized children (1-3). Mortality from AKI in pediatric intensive care units ranges from 9% - to as high as 67% (4-7). Incidence of AKI, associated mortality and morbidity is increasing worldwide (8, 9). An Indian study showed an incidence of 9% in the general ward and 36% in the critically ill children (9).

In developing countries the commonest causes of acute kidney injury include fluid loss, infection, primary renal diseases like glomerulonephritis, hemolytic uremic syndrome and nephrotic syndrome. In hospitalized children secondary causes are the common causes of acute kidney injury like heart disease, infection, nephrotoxic drugs and perinatal asphyxia (10, 11).

The most important principle in the management of acute kidney injury is prevention. Identification of hospitalized children with high risk of developing acute kidney injury and early intervention at an earlier stage of the kidney injury might reverse the process. In potentially high risk hospitalized children drug dosages have to be closely watched and in potentially nephrotoxic medications alternative drugs have to be considered and/or dose adjustments have to be made.

The magnitude of acute kidney injury in hospitalized children in our context is not known. Identifying the incidence of the problem and factors associated with acute kidney injury will give us directions for planning in the prevention and early detection of acute kidney injury in high risk patients.

II. Materials and methods

Study design: This was a prospective, institution based and observational study conducted among children between the ages of 1 month and 14 years, admitted to pediatric inpatient and emergency units.
Study location: This was a tertiary care university hospital located at the capital city of Ethiopia, Addis Ababa.
Study duration: July 2016 to February 2017.
Sample size: All children admitted during the study period were included
Study procedure and tools: Eligible children who developed AKI and the same number of adjacently registered eligible children who didn't develop AKI were included in the study. Data collection was using a structured questionnaire developed to extract, the background of the child and its care taker from the chart in a

child who had normal renal function at admission and developed abnormal renal function test after 24 to 48 hrs of admission. Record reviewing on medication and laboratory investigation related to urine analysis, creatinine level and other routine laboratory investigation from the child's recording chart was done. The second assessment of data collection was undertaken after 24-48 hours of the diagnosis of AKI and then when necessary and patients were followed up until death or discharge. The questionnaire was developed based on the objectives of the study and the data collection was undertaken by the first investigator.

Inclusion criteria

All children admitted for any medical illness other than the kidney, age between one month to 14 years and abnormal renal function test detected after 24-48 hour of admission were included.

Exclusion criteria

The following children were excluded: I) children with known acute or chronic kidney disease at admission; ii) hospital stay for less than 24 h; iii) serum creatinine not done at admission or at 48 h; iv) age less than one month and >14 years.

Data analysis

Data from the questionnaire and checklist was assessed for completeness, and entered into a computer, using epi-data version 3.0 computer software. The data was exported to SPSS for windows, for cleaning and further analysis. The cleaned data was transformed into meaningful variables, and simple descriptive and analytic analysis was done. During descriptive analysis, frequency distribution, proportions and including central tendency and dispersion was made as appropriate. Both cumulative incidence and incidence density was calculated using proportion of new cases against children included in the study, and proportion of new cases against person time study subjects observed at risk. For the analytic study, bivariate analysis was made between determinant variables against the outcome using cox regression. Determinant variables having association with both the outcome during the bivariate analysis were included in a model for the multivariate analysis to suppress the confounding effect. Similarly, stratified analysis was made to assess for effect modification of some determinant variables. Finally, the study assessed the survival rate of children who acquired acute kidney injury against other children with common childhood illness. Findings was illustrated using tables, proportions and 95% confidence levels, figures and graphs as appropriate. A p-value of, 0.05 was considered to be statistically significant.

Definition

Based on the AKIN (acute kidney injury network) criteria, AKI was defined as abrupt (if sustained within 48 hrs) reduction in kidney function with an increase in creatinine level. The illness was categorized as stage 1 (an increase of creatinine by ≥0.3 mg/dL, or increase to 1.5-1.99 times of the baseline), stage 2 (increase to 2–2.99 times of the baseline) and stage 3 (increase to≥3 times the baseline, or≥4 mg/dL with an acute rise of > 0.5 mg/dL) (13, 14). The urine output criterion was not used for defining acute kidney injury.

Complete recovery was defined when the patient has a normal blood pressure, urinalysis and a normal serum creatinine for age (0.2-0.4 mg/dl for infants, 0.3-0.7 mg/dl for children 1-12 years of age; 0.5-1mg/dl for children 13-18 years)(12). Partial recovery was the presence of hypertension, abnormal urinalysis, and a level of creatinine that didn't decrease to the normal range in the treatment period.

Ethical consideration

Clinical evaluation of patients and all investigations were done as a routine for every patient who is admitted to the emergency unit and to the wards then after. It did not involve human subjects and did not incur any harm to the patient. Any child found with abnormal renal function study was managed by the pediatric nephrologist. For this reason consent was not required from guardians. Confidentiality of the patient information was exercised. Ethical clearance was obtained from the Department of Pediatrics and Child Health Research and Publication committee and Institutional Review Board of the College of health Sciences, Addis Ababa University.

III. Results

Of 5348 admissions, 68 children developed AKI and 69 adjacently registered children without AKI were controls. Of the cases and controls; 62.0% were between the ages of one month and4years with a mean age of 4.53+4.37. Males were 59.1%. The common diagnoses at admission were malignant diseases (28.5%), congestive heart failure (17.5%), sepsis (9.5%), and other conditions (pneumonia, acute surgical conditions, neurologic diseases, gastrointestinal infections, congenital heart diseases, diabetes mellitus, malnutrition, foreign bodies in the aero-digestive tract). No statistical difference was seen between the study subjects and the source population in age and sex (P > 0.5) (table 1).

Table 1: Socio-demographic characteristics of study subjects (n=137)

Characteristics	Study population		Source population		X^2
	Number	Percent	Number	Percent	(p-Value)
Age group					
1mon* -4 years	85	62.0	3398	63.5	X^2 = 0.128 (P>0.5)
5-14 years	52	38.0	1950	36.5	
Mean + SD	4.53+ 4.37				
Sex					
Male	81	59.1	3301	61.7	X^2 = 0.3819 (P>0.5)
Female	56	40.9	2047	38.3	
Diagnosis at admission					
Heart failure	24	17.5	-	-	-
Malignant diseases	39	28.5	-	-	-
Sepsis	13	9.5	-	-	-
Others**	61	44.5	-	-	-

*mon: month, **others= (pneumonia, acute surgical conditions, neurologic diseases, gastrointestinal infections, congenital heart diseases, diabetes mellitus, malnutrition, foreign bodies in the aero-digestive tract)

The overall incidence of AKI was 12.7/ 1000 admissions (95% CI, 9.96-16.0) in the study period. When categorized by age, the incidence for less than 5 years and 5 to 14 years were 11.5/1000 and 14.9/1000 respectively. The incidence was 17.6/1000 among females and 9.7/1000 among males. Of all the AKI cases, the proportion of severe AKI (stage 2 and 3) was 64.7%.

The overall cause specific death rate was 5.8% (4.74 percent in under five years and 8.08 percent among 5 to 14 years of age). Among females and males, it was 8.46 and 3.89 percent respectively. Of the 68 children with AKI there were 18 deaths, with case fatality rate of 26.5% (95% CI 17.03-37.88) compared to 8.7% without AKI (controls). Among AKI associated deaths, 27.6% were children between 5 to 14 years of age and female deaths were 30.6%. Malignant diseases accounted for 34.6%, sepsis 30.0% and heart failure 14.3% of the AKI associated deaths, (Table 2).

Table 2: Incidence and cause specific death rate of children admitted to department of pediatrics, at a tertiary hospital, Addis Ababa, 2018

	Population	Cases	Incidence per 1000	(95% CI per 1000)
Morbidity				
Age group				
1 mon-4 years	3398	39	11.5	(8.3-15.5)
5-14 years	1950	29	14.9	(10.2-21.0)
Sex				
Male	3301	32	9.7	(6.75- 13.5)
Female	2047	36	17.6	(12.5- 24.0)
Overall	5348	68	12.7	(9.96- 16.0)
Mortality(Cause specific death rate)			Percent	
Age group				
1 mon*-4 years	211	10	4.74	(2.43-8.28)
5-14 years	99	8	8.08	(3.82-14.8)
Sex				
Male	180	7	3.89	(1.71- 7.54)
Female	130	11	8.46	(4.5- 14.6)
Overall	310	18	5.81	(3.59- 8.85)
Mortality (Case fatality rate)			Percent	
Age group				
1 mon*-4 years	39	10	25.64	(13.82-40.96)
5-14 years	29	8	27.59	(13.71-45.75)
Sex				
Male	32	7	21.88	(10.10- 38.55)
Female	36	11	30.56	(17.24- 46.90)
Diagnosis at admission				
Congestive heart failure	14	2	14.3	(2.47- 39.7)
Malignant diseases	26	9	34.6	(18.4- 54.1)
Sepsis	10	3	30.0	(8.3- 62.0)
Others**	18	4	22.2	(7.5- 45.3)
Overall	68	18	26.47	(17.03- 37.88)

*mon: month; **others include: Others include: pneumonia, acute surgical conditions, neurologic diseases, gastrointestinal infections, congenital heart diseases, diabetes mellitus, malnutrition

Cox regression analysis was done for age, sex and diagnosis at admission as risk factors for AKI. Age 5-14 years had a 1.2 times higher risk of developing AKI than children under five years (adjusted HR 1.22; 95% CI, 0.74-2.98). Female gender had 2.8 times higher risk of developing AKI (adjusted HR 2.79; 95% CI, 1.29-6.02) than male gender. Children with heart failure, malignant diseases and sepsis had 3.7 times, 4.5 times and 8.0 times higher risk of developing AKI than other diagnosis respectively with (AHR 3.74; 95% CI, 1.34-10.4), (AHR 4.50; 95% CI, 1.78-11.4) and (AHR 8.09, 95% CI, 1.88-34.8) respectively. Table 3 shows risk factors for developing AKI.

Table 3: Hazard ratio of risk factors for AKI in children admitted to department of pediatrics, at a tertiary hospital, Addis Ababa, 2018

Characteristics	Developed AKI			
	Case (%)	Not-case (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age group				
1-4 years	39 (45.9)	46 (54.1)	1.00	1.00
5-14 years	29 (55.8)	23 (44.2)	1.49 (0.74, 2.98)	1.22 (0.54, 2.78)
Sex				
Male	32 (39.5)	49 (60.5)	1.00	1.00
Female	36 (64.3)	20 (35.7)	2.76 (1.36, 5.58)	2.79 (1.29, 6.02)
Diagnosis at admission				
Heart failure	14 (58.3)	10 (41.7)	3.34 (1.26, 8.92)	3.74 (1.34, 10.4)
Malignant diseases	26 (66.7)	13 (33.3)	4.78 (2.01, 11.3)	4.50 (1.78, 11.4)
Sepsis	10 (76.9)	3 (23.1)	7.96 (1.96, 32.4)	8.09 (1.88, 34.8)
Others*	18 (29.5)	43 (70.5)	1.00	1.00

* Others include: pneumonia, acute surgical conditions, neurologic diseases, gastrointestinal infections, congenital heart diseases, diabetes mellitus, and malnutrition

Children with AKI had 1.8 times higher risk of dying when compared with controls (AHR 1.82, 95%CI, 0.68-4.87). Under five years of age and female gender didn't contribute any difference in the mortality rate between AKI and controls (AHR 0.73, 95% CI 0.26-2.01) and (AHR 1.44, 95%CI, 0.58-0.55), respectively. However, malignant diseases with AKI had 3 times higher risk of death when compared with controls (AHR 3.31, 95% CI, 1.09-10.1).

The mortality rate in children with AKI stage 1 (n=24), stage 2 (n=21), stage 3 (n=23) was 16.7%, 19.0% and 39.1% respectively. Death rate from severe kidney injury was 31.8% (stage 2 and 3, n=44)) versus stage one 16.7% (n=24). Children with severe AKI had 3 times higher risk of death than non-severe AKI (AHR 3.03, 95% CI, 0.76-12.0 (Table 4).

Table 4: Adverse outcome (death) of children with AKI and controls admitted to department of pediatrics, at a tertiary hospital, Addis Ababa, 2018

Characteristics	Adverse outcome			
	Death (%)	No death (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age group				
1-4 years	16 (18.8)	69 (81.2)	1.00	1.00
5-14 years	11 (21.2)	41 (78.9)	1.16 (0.49, 2.73)	0.73 (0.26, 2.01)
Sex				
Male	13 (16.0)	68 (84.0)	1.00	1.00
Female	14 (25.0)	42 (75.0)	1.74 (0.75, 4.07)	1.44 (0.58, 3.55)
Diagnosis at admission				
Heart failure	2 (8.3)	22 (91.7)	0.60 (0.12, 3.07)	0.53 (0.10, 2.80)
Malignant diseases	14 (35.9)	25 (64.1)	3.71 (1.38, 9.99)	3.32 (1.09, 10.1)
Sepsis	3 (23.1)	10 (76.9)	1.99 (0.45, 8.81)	1.33 (0.27, 6.41)
Others*	8 (13.1)	53 (86.9)	1.00	1.00
Developed AKI				
Yes	18 (26.5)	50 (73.5)	2.40 (0.99, 5.81)	1.82 (0.68, 4.87)
No	9 (13.0)	60 (87.0)	1.00	1.00
Severity of AKI				
Severe (2-3)	14 (31.8)	30 (68.2)	3.11 (1.21, 8.01)	2.68 (0.96, 7.47)
Non-severe	4 (16.7)	20 (83.3)	1.33 (0.37, 4.81)	0.85 (0.20, 3.56)
No AKI	9 (13.0)	60 (87.0)	1.00	1.00
Severity among AKI cases				
Severe (2-3)	14 (31.8)	30 (68.2)	2.33 (0.67, 8.12)	3.03 (0.76, 12.0)
Non-severe	4 (16.7)	20 (83.3)	1.00	1.00

*Others include: pneumonia, acute surgical conditions, neurologic diseases, gastrointestinal infections, congenital heart diseases

Among 20 survivors from stage 1, 14 children recovered completely, 3 children partially and another 3 remained the same. Among 17 survivors of stage 2, 11 recovered completely, 2 children partially and 4

remained the same. Among 13 survivors of stage 3, 10 completely recovered but 3 had partial recovery at the time of discharge. All partially recovered children had elevated creatinine levels.

IV. Discussion

When the age and sex distribution of the study subjects were compared with the total admissions there was no statistically significant difference ($p > 0.05$) indicating that there was no bias in selecting study subjects.
The incidence of AKI in our cohort of children was 12.7 per 1000 admissions. Sepsis, malignant diseases, congestive heart failure, and female gender were risk factors for AKI. In studies done using the AKIN criteria in hospitalized children, the incidence of AKI ranged from 4.6-9.9 per 1000 admissions (3). Our finding was similar to these reports. The incidence of pediatric AKI depends on the criteria used, AKIN or pRIFLE and critically ill (ICU) and non-critically ill patients. Studies have shown higher incidences (17.9-52%) using the pRIFLE criteria in ICU patients (15-18).

In this study AKI was associated with female gender and increasing age; the highest incidence was in children 5 to 14 years of age. A national AKI incidence report by Scott M. Sutherland et.al (19) showed the highest incidence was among 15-18 years of age. This is similar with our report but several other studies have contrasting reports, which found young age to be associated with the highest incidence of AKI (20-21).
The etiologies of AKI vary from place to place. In our previous case series in hospitalized children, hemolytic uremic syndrome was the commonest cause of AKI followed by acute post infectious glomerulonephritis and serious systemic infections (22). In developed countries major surgeries, malignancies and nephrotoxic medications are causes of AKI (23, 24). Since the objective of the current study was to determine the incidence of acute kidney injury in hospitalized children, we excluded known cases of AKI.

Reports of mortality rate following AKI vary depending on the severity of the underlying illness and the criteria used to define AKI. Mortality rates ranging from 9 to 67% were reported (25-29). In the present study mortality was 26.5%. The death rate was higher in severe AKI (stage 2 and 3) than stage 1 AKI. The presence of acute kidney injury was responsible for a 3-fold increase in mortality when compared with controls. Our findings are comparable with the above reports. Malignancy and Sepsis associated AKI had the highest mortality. It seems that the severity of the underlying illness is responsible for high mortality in our AKI cohort.
Over half of the children with stage 1 AKI recovered completely, the remaining had partial recovery and some were discharged in the same condition. More than half of the survivors from stage 2 and 3 AKI have recovered completely at the time of discharge but some remained the same. These children require longer time of follow up to examine outcomes but this was not the scope of this study.

Limitations of this study include: the diagnosis of AKI was based on the creatinine criteria but it didn't include the urine out that might have under reported the incidence. This study was conducted in a single institution where very sick patients that are referred from other hospitals are being admitted. It would be important to conduct a multi-center study that would be representative. We lack data in children who had partial recovery or remained the same at the time of discharge to assess the outcome of AKI.

V. Conclusion and recommendations

Acute kidney injury is common in hospitalized children and it is a significant cause of mortality. Prevention in high risk groups, early diagnosis and treatment improves the outcome. We recommend multi-center studies to be conducted.

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