RESEARCH PAPER

Incidence of Acute Kidney Injury in Hospitalized Children

POONAM MEHTA, ADITI SINHA, ABDUS SAMI, PANKAJ HARI, *MANI KALAIVANI, ASHIMA GULATI, MADHULIKA KABRA, SUSHIL K KABRA, RAKESH LODHA AND ARVIND BAGGA

*From the Departments of Pediatrics and *Biostatistics, All India Institute of Medical Sciences, New Delhi, India.*

Correspondence to: Dr Aditi Sinha, Division of Nephrology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. aditisinha4@rediffmail.com

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Objective: To determine the incidence and outcome of acute kidney injury (AKI) in hospitalized patients.

Design: Prospective, observational.

Setting: Tertiary care center in North India.

Participants/patients: Inpatients, 1 month to 18-yr-old.

Intervention: None.

Main Outcome Measures: Incidence of AKI based on the serum creatinine criteria proposed by the AKI Network.

Results: During February to September 2008, thirty nine of 108 (36.1%) critically ill patients and 34 of 378 (9.0%) patients who were not critically ill developed AKI (*P* <0.001); the respective incidence densities were 45.1 and 11.7 cases/1000 patient days, respectively. The maximal stage of AKI was stage 1 in 48 (65.8%) patients, stage 2 in 13 (17.8%) and stage 3 in 12 (16.4%) patients; 11 (15.1%) required dialysis. Patients with AKI had a significantly longer duration of hospital stay (9 days *vs* 7 days, *P*<0.02) and higher mortality (37% *vs* 8.7%; hazard ratio, HR 2.73; 95% CI 1.64, 4.54). Independent risk factors for AKI were young age (HR 0.89; 95% CI 0.83, 0.95), shock (HR 2.65; 95% CI 1.32, 5.31), sepsis (HR 3.64; 95% CI 2.20, 6.01), and need for mechanical ventilation (2.18; 95% CI 1.12, 4.26). Compared to patients without AKI, the mortality was higher for AKI stage 2 (HR 5.18; 95% CI 2.59, 10.38) and stage 3 (HR 4.34; 95% CI 2.06, 9.16). Shock was an independent risk factor for mortality (HR 10.7; 95% CI 4.96, 22.98).

Conclusions: AKI is common in critically ill children, especially younger patients with septicemia and shock, and results in increased hospital stay and high mortality.

Key words: *Acute Kidney Injury Network, Acute tubular necrosis, Dialysis, India.*

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Acute kidney injury (AKI) is an important condition in hospitalized patients, associated with adverse short- and long term outcomes [1,2]. Mortality rates in critically ill children with AKI are high, ranging between 9% and 67% [3,4] and increase if complicated by multiorgan failure, organ transplantation and acute respiratory distress syndrome [1, 5]. Most cases of incident AKI represent acute tubular necrosis (ATN) that is secondary to hypovolemia, sepsis or the use of nephrotoxic agents [1,6].

Recent reviews emphasize that disparities in the definition of AKI have resulted in large variations in reported incidence and outcomes [1,6]. The definition and staging of AKI has been recently standardized using the RIFLE classification proposed by the Acute Dialysis Quality Initiative Group [7], and the one suggested by the Acute Kidney Injury Network (AKIN) [8]. These classifications have been examined in hospitalized adults [9,10] and children [3,11-15], and found useful in characterizing AKI.

Most pediatric studies on the incidence of AKI are limited to the developed countries [3,11-12,14,16] and are based on retrospective analysis of records [3,12]. Given that the spectrum of AKI differs in developing countries and that retrospective ascertainment of diagnosis is difficult, we aimed to prospectively determine the incidence and course of AKI in children hospitalized at a tertiary care center in North India.

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METHODS

This prospective study was carried out on consecutive patients, between the ages of 1 month and 18 years, admitted to the Pediatric inpatient and Pediatric intensive care unit (PICU) at the All India Institute of Medical Sciences, New Delhi from February to September 2008. The following patients were excluded: (*i*) chronic kidney disease stage 5 (estimated glomerular filtration rate <15 mL/min/1.73 m^2) [17];(*ii*) bilirubin level >5 mg/dL; (*iii*) hospital stay for less than 24 h; (*iv*) known AKI at admission, with serum creatinine >1.5 mg/dL; and (*v*) serum creatinine not done at admission or at 48 h.

The study was approved by the Institute Ethics Committee. Following informed parental consent, information regarding the diagnosis, comorbidities and duration of hospital stay were recorded. The Pediatric Index of Mortality score version 2 (PIM2) was computed for patients admitted to the PICU [18]. Patients were classified as (critically ill) if they were admitted to the PICU, required mechanical ventilation or vasopressor support (need for dopamine and/or dobutamine at a dose exceeding 10 µg/kg/minute, and/or adrenaline at any dose for management of hypotension). Patients who did not meet these criteria were considered (not critically ill).

Serum levels of creatinine were estimated on Hitachi 717 autoanalyzer by modified Jaffe method [19], at admission and thereafter every 24±6 h for 3 consecutive days in all patients. Subsequently, the estimation was done at daily intervals in patients with AKI and in the critically ill. In those not critically ill, but having risk factors (features of dehydration, congestive heart failure or shock; therapy with diuretics or nephrotoxic agents [20]; new onset sepsis), these levels were determined every 48±6 h until discharge.

Based on the AKIN criteria, AKI was defined as abrupt (within 48 h) reduction in kidney function with an increase in creatinine level [8]. The illness was categorized as stage 1 (increase of creatinine by ≥0.3 mg/dL, or to 1.5-1.99 times baseline), stage 2 (increase to 2–2.99 times baseline) and stage 3 (increase to ≥3 times baseline, or ≥4 mg/dL with an acute rise of >0.5 mg/dL) [8]. The urine output criterion was not used for defining or staging AKI. Shock was defined in presence of tachycardia, feeble pulses, cool peripheries, hypotension (blood pressure <-2 SD for age and sex) or capillary filling time >3 seconds [21]. Sepsis was the presence of systemic inflammatory response syndrome with suspected or proven infection [21].

The patients were evaluated to ascertain the etiology of AKI, its progression and need for dialysis. They were followed until discharge and the outcome was examined in relation to the maximal stage of AKI. ATN was defined as renal dysfunction, in a setting of diarrhea with dehydration, blood loss, cardiac dysfunction, sepsis, burns or use of nephrotoxic agents, in the absence of active urinary sediment. Acute interstitial nephritis was considered in patients with leukocyturia and suggestive renal histology.

Complete recovery was defined as normal urinalysis and blood pressure, and normal serum creatinine for age (0.2-0.4 mg/dL for infants; 0.3-0.7 mg/dL for 1-12 yr; 0.5-1.0 mg/dL for 13-18 yr) [22]. Partial recovery was the presence of hypertension, abnormal urinalysis (>1+ proteinuria, urine protein to creatinine ratio >0.2 mg/mg; >5 leukocytes or red cells per high power field) or elevated serum creatinine. Patients requiring maintenance dialysis were classified as dialysis dependent.

Statistical analysis: The incidence of AKI in children is approximately 5% among non-critically ill [16,23] and 30% in critically ill [1,5]. In order to estimate these incidence rates at 95% confidence, and precision of 2.5% for the non-critically ill and 9% for critically ill, the required sample sizes were 304 and 104, respectively.

Results were analyzed using STATA software version 11 (College Station, TX). Continuous data were expressed as median (interquartile range, IQR) and categorical variables as number (%). The incidence density (95% confidence interval, CI) was the number of cases per 1000 patient days. Patient characteristics between groups were compared using Fisher exact test or Wilcoxon rank-sum test. Mortality was compared in patients with and without AKI using the log rank test. Risk factors for AKI and mortality were examined using Cox proportional hazard analysis and reported as hazard ratio (95% confidence interval, CI).

RESULTS

Of 613 patients screened, 127 were excluded (***Fig.* 1**), including 28 patients admitted with a diagnosis of AKI, secondary to rapidly progressive glomerulonephritis (9), hemolytic uremic syndrome (7), dehydration (7) and septicemia (5).

Of 486 patients, 108 (22.2%) were critically ill and 378 (77.8%) were non-critically ill (***Table* I)**. Among critically ill patients, the PIM2 scores at admission were 10.7 (5.4-21.6). The common diagnoses at admission were pneumonia or asthma (22.6%), malignancy (16.7%), neurological illness (14.6%) and renal diseases (9.5%).

Incidence and etiology

Seventy three (15.0%) patients, including 39 who were critically ill, developed AKI at a median (IQR) of 2 (2-3) days. The incidence of AKI was 36.1% in the critically ill patients and 9.0% in the non-critically ill (P <0.001). The overall incidence density of AKI was 19.4 (95%, CI 15.42, 24.39) cases per 1000 patient days. The incidence density was higher for critically ill patients (45.1; 95% CI 3.3, 61.78 cases per 1000 patient days) than the non-critically ill (11.7; 95% CI 8.37, 16.4 cases per 1000 patient days).

The most common etiology of AKI was considered to be ATN (n=70, 95.9%), both in critically ill (n=39) and non-critically ill patients (n=31). Other causes were acute

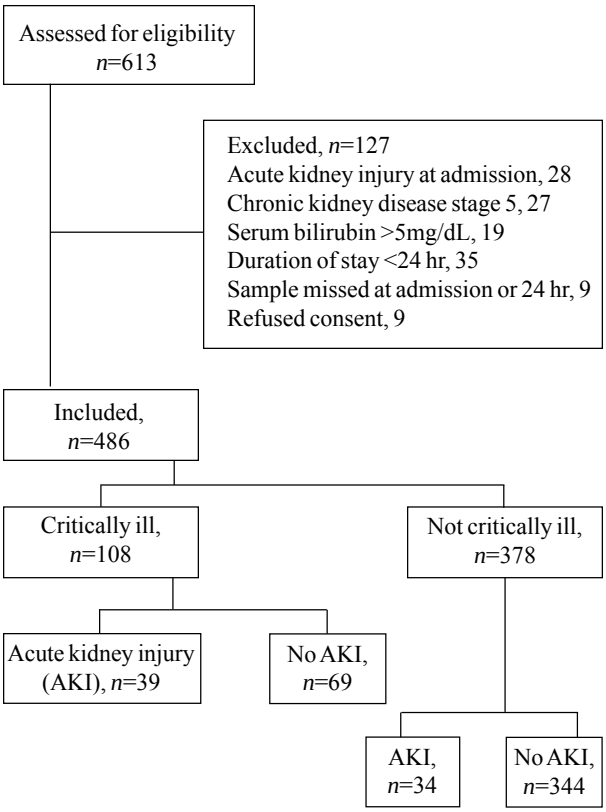

FIG.1 *Flow chart showing the details of patients recruited into the study.*

TABLE I BASELINE CLINICAL AND BIOCHEMICAL CHARACTERISTICS (*N*=486)

Characteristics	*Critically ill (n=108)*	*Non-critically ill (n=378)*
Age, mo	43 (9-72)	48 (12-96)
Girls	43 (39.8)	132 (34.9)
Blood creatinine, mg/dL	0.5 (0.4-0.6)	0.5 (0.4-0.6)
Diagnosis at admission		
Pneumonia, asthma	31 (28.7)	79 (20.9)
Malignancy	19 (17.6)	62 (16.4)
Neurological illness	23 (21.3)	48 (12.7)
Heart disease	10 (9.3)	9 (2.4)
Renal disease*	1 (0.9)	45 (11.9)
Liver disease	4 (3.7)	25 (6.6)
Gastroenteritis	4 (3.7)	12 (3.2)
Connective tissue disease	1 (0.9)	13 (3.4)
Immunodeficiency	1 (0.9)	10 (2.6)
Dengue	4 (3.7)	7 (1.9)
Malaria	1 (0.9)	6 (1.6)
Others	9 (8.3)	62 (16.4)

*Values for continuous variables are expressed as median (interquartile range); categorical variables are expressed as number (%); *nephrotic syndrome, glomerulonephritis, obstructive uropathy*

interstitial nephritis (*n*=2) and bladder outlet obstruction (*n*=1). Sepsis (*n*=42, 60%) and shock (*n*=38, 54.3%) were the chief predisposing conditions for ATN; other factors, alone or in combination, were nephrotoxic agents (*n*=14), congestive heart failure (*n*=7), diarrheal dehydration (*n*=6) and blood loss (*n*=3).

Clinical features

***Table* II** shows that patients with AKI were younger than those without AKI (*P*=0.002). They also had significantly higher frequencies of shock, sepsis and need for vasopressor support and mechanical ventilation. Critically ill patients with AKI tended to have higher PIM2 scores than those without AKI (*P*=0.08).

AKI stage 1 was detected in 60 patients, stage 2 in 11 and stage 3 in two patients. Five and 7 patients from stage 1 AKI progressed to stages 2 and 3, respectively, while three patients advanced from stage 2 to stage 3. The maximal stages of AKI were stage 1 in 48, stage 2 in 13 and stage 3 in 12 patients. Eleven (91.7%) patients with AKI stage 3 required peritoneal dialysis (*n*=8) or hemodialysis (*n*=3), starting 3 to 20 days after hospital admission. The median duration of hospital stay was 9 (6-13) days for patients with AKI compared to 7 (5-10) days for those without AKI (*P*=0.02).

TABLE II CHARACTERISTICS OF PATIENTS WITH AND WITHOUT ACUTE KIDNEY INJURY

Characteristic	*Acute kidney injury (n=73)*	*No acute kidney injury (n=413)*
Age, mo	24 (7-60)	48 (12.5-96)
Girls	30 (41.1)	145 (35.1)
Diagnoses at admission		
Pneumonia	21 (28.8)	82 (19.9)
Malignancy	11 (15.1)	70 (17.0)
Neurological illness	10 (13.7)	61 (14.8)
Heart disease	4 (5.5)	15 (3.6)
Renal disease*	7 (9.6)	39 (9.4)
Mechanical ventilation#	35 (48.0)	58 (14.0)
Shock#	38 (52.1)	98 (23.7)
Sepsis#	42 (57.5)	124 (30.0)
Vasopressor support#	29 (39.8)	62 (15.0)
PIM2 score (in PICU)	13.1 (7.9-25.2)	9.1 (4.9-16.7)
Mortality#	27 (37.0)	36 (8.7)

*Values for continuous variables are expressed as median (interquartile range); categorical variables are expressed as number (%); *Nephrotic syndrome, glomerulonephritis, obstructive uropathy; #P<0.001; $P=0.002.*

Outcome

Sixty three patients died after a median duration of 8 (range 2-49) days. A higher proportion of critically ill patients died (60 of 108; 55.5%) compared to those not critically ill (3 of 378; 0.8%). The mortality in patients with and without AKI was 37.0% and 8.7%, respectively. The mortality in patients with AKI stage 1 (n=7, 14.6%) was lower compared to stage 2 (n=11, 84.6%) and stage 3 (n=9, 75%) (P<0.001).

Among 41 survivors with AKI stage 1, 22 showed complete recovery. Of 19 patients with partial renal recovery, 11 had abnormal urinalysis, and 5 each showed hypertension and elevated serum creatinine. Of 2 patients with AKI stage 2, one each showed complete and partial renal recovery at discharge. One patient each with AKI stage 3 showed complete and partial renal recovery, and one was dialysis dependent.

On Cox regression analysis, independent risk factors for AKI included young age and presence of shock, sepsis and need for mechanical ventilation (P<0.001) (***Table* III**). On univariate analysis, risk factors for mortality were shock (HR 11.93; 95% CI 5.64, 25.25; P<0.001) and presence of AKI (2.73; 95% CI 1.64, 4.54; P<0.001). Compared to patients without AKI, the risk of mortality was higher for AKI stage 2 (HR 5.18; 95% CI 2.59, 10.38; P<0.001) and stage 3 (HR 4.34; 95% CI 2.06, 9.16; P<0.001), but not for stage 1 (HR 1.23; 95% CI 0.54, 2.80; P 0.62). On Cox regression, shock was the only independent risk factor for mortality (HR 10.7; 95% CI 4.96, 22.98; P<0.001).

DISCUSSION

This prospective study, from a referral center in North India, found that the incidence density of AKI in hospitalized patients was 19.4 cases per 1000 patient days. The incidence was 4-fold higher in critically ill patients compared to the non-critically ill. While most patients initially showed stage 1 disease, there was progressive kidney dysfunction, and 15.1% required renal replacement therapy. Younger patients and those with sepsis, shock and mechanical ventilation were at increased risk for AKI. The presence of AKI resulted in prolonged hospital stay and a four-fold higher mortality, especially among patients with AKI stages 2 and 3.

TABLE III RISK FACTORS FOR ACUTE KIDNEY INJURY

Risk factor	*Hazard ratio (95% confidence interval)*	
	Unadjusted	*Adjusted*
Age, y	0.91 (0.81, 0.97)*	0.89 (0.83, 0.95)*
Female gender	1.23 (0.80, 2.02)	1.16 (0.72, 1.87)
Shock	2.85 (1.80, 4.52)**	2.65 (1.32, 5.31)*
Sepsis	2.75 (1.73, 4.37)**	3.64 (2.20, 6.01)**
Mechanical ventilation	4.12 (2.60, 6.52)**	2.18 (1.12, 4.26)*

*$P<0.05$, **$P<0.001$

Two recently proposed classifications, the RIFLE [7] and AKIN [8] criteria have been validated as diagnostic and prognostic tools in critically ill adult patients with AKI [9, 10]. Studies in critically sick children, using the RIFLE [12] or its pediatric modification, pRIFLE [3, 14], show that the incidence of AKI varies from 10% to 58%. Based on the former, Schneider, *et al*. [12] reported that 339 of 3396 (10%) patients admitted to a PICU in Los Angeles had AKI. The AKIN criteria have been used in three recent studies in children [13-15]. Zappitelli, *et al* reported that the incidence of AKI in hospitalized children treated with aminoglycosides was 20% by the AKIN definition and 33% by pRIFLE [14]. Although these criteria were used in other studies, [14,15] neither study reported on its incidence. Using similar criteria, we found that more than one-third of all critically ill patients showed incident AKI. While there is limited information on AKI among hospitalized, non-critically ill patients [16,19], the present study showed an incidence of 9%. Based on present and previous reports, independent risk factors for AKI were young age, hypotension and sepsis, and the need for mechanical ventilation [1,3,15].

The etiology of AKI in children varies in developed and developing countries. In the former, AKI follows major surgeries, complications associated with malignancies and the use of nephrotoxic drugs [1,6]. In developing countries, hemolytic uremic syndrome, severe systemic infections, diarrheal dehydration, and postinfectious glomerulonephritis constitute important causes [7, 24]. Since the present study aimed to determine the incidence of AKI in hospitalized children, we excluded patients with a known diagnosis of AKI at admission. However, it is notable that apart from the 73 patients (15%) with incident AKI, 28 patients (5.5%) were admitted with a diagnosis of AKI secondary to hemolytic uremic syndrome, septicemia, rapidly progressive glomerulonephritis, and dehydration. Comparable findings were reported by Schneider, *et al.* [12] where the rates of AKI at admission and that developing during hospital stay were 5.7% and 10%, respectively.

The occurrence of AKI has significant implications, with considerable short and long term morbidity and mortality [1,2]. Almost 6-45% of critically sick patients with incident AKI require renal replacement therapy, as was confirmed in the present study [5,11,13,15]. The risk of mortality varies, reflecting the heterogeneous criteria

WHAT IS ALREADY KNOWN?

- Acute kidney injury (AKI) is common in hospitalized critically ill children and is associated with increased mortality

WHAT THIS STUDY ADDS?

- Incident AKI affects almost one-third of critically sick and 10% of non-critically sick hospitalized children.
- Risk factors for AKI include young age, shock, sepsis and need for mechanical ventilation
- Higher stages of AKI are associated with increased mortality and prolonged hospital stay.

used for definition, and the spectrum and severity of the underlying illness. Compared to rates between 9 to 67% in various reports [3,4,11-13,15], mortality was 37% in the present study. Furthermore, we found that the risk of mortality was higher in patients with AKI stages 2 and 3 than in those without kidney injury. While data from multiple studies suggest that AKI is an independent risk factor for mortality [5,11,13,15], these findings were not confirmed in the present study. We speculate that the severity of underlying illness and the presence of hypotension in these patients predisposed to death more strongly than incident AKI.

Almost half of the patients with stage 1 AKI recovered completely, and the other survivors showed partial recovery at the time of discharge. While the present study was underpowered to examine outcomes in different grades of AKI, it is possible that minor grades of renal injury have fewer implications than more significant changes in renal function.

The present study has multiple limitations. Precise measurements of urine output were not done and the diagnosis of AKI was based only on levels of serum creatinine. While some studies [10,11,25] suggest that criteria based on urine output have little effect on assignment of the final AKI stage and its association with outcomes, this might have resulted in underreporting of the incidence. Secondly, this study was performed at a single center, on patients who were sicker and many had chronic morbidities. It would be necessary to confirm the incidence of AKI in hospitalized children in other settings. Neonates were excluded in this study since their susceptibility and etiology of AKI is considerably different from older infants and children. Exclusion of patients with serum creatinine above 1.5 mg/dL may have resulted in erroneous exclusion of patients with unknown but early chronic kidney disease. The present study was not powered to examine risk factors for mortality, and larger studies that address these risk factors are necessary. Finally, the lack of information on outcomes after discharge does not allow assessment of the impact of mild AKI on short and long-term renal function.

This prospective study provides data on the incidence of AKI in hospitalized children. It emphasizes that the incidence of AKI is high in patients who are critically sick, especially young children with shock, sepsis and those requiring mechanical ventilation. The presence of AKI resulted in prolonged hospital stay and increased mortality. Further studies are required to examine the short- and medium-term impact of AKI on renal outcome.

Contributors: AB and ASi conceived and designed the study, analyzed the data and were directly involved in paper writing; AB would act as guarantor; PM and AS were responsible for data collection; PM also contributed to analysis and drafting of the paper; MK provided statistical inputs; RL, MKb, SKK, PH and AG participated in protocol development and implementation of the study.
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