RESEARCH PAPER

Etiology and Outcome of Community-Acquired Acute Kidney Injury in Pediatric Inpatients

Ashna Ashish, Manish Kumar, Kirtisudha Mishra
Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, Delhi.

Correspondence to:
Dr Manish Kumar,
Room No 403, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110 031.
manishkp75@yahoo.com
Received: Sept 13, 2022;
Initial review: Nov 09, 2022;
Accepted: Mar 05, 2023.

Objective: To estimate the etiology, outcome, and risk factors for mortality in children with community-acquired acute kidney injury (CA-AKI). **Methods:** Between October, 2020 and December, 2021, consecutive hospitalized children aged 2 mo-12 years with a minimum 24 hours of stay, and at least one serum creatinine level measured at or within 24 hours of hospitalization were prospectively enrolled. CA-AKI was labelled in children with an elevated serum creatinine level at admission and subsequent fall during hospitalization. **Results**: Of 2780 children, 215 were diagnosed as CA-AKI (7.7%, 95% CI 6.7-8.6). Diarrhea with dehydration (39%) and sepsis (28%) were the most common causes of CA-AKI. 24 children (11%) died during hospitalization. Requirement of inotropes was an independent predictor of mortality. Out of 191 children discharged, 168 (88%) had complete renal recovery. At 3 months, out of 22 children without complete renal recovery, 10 progressed to chronic kidney disease (CKD), with 3 becoming dialysis dependent. **Conclusions:** CA-AKI is common in hospitalized children, and is associated with increased risk of progression to CKD, especially in those with incomplete renal recovery.

Keywords: *Chronic kidney disease, Inpatient, Outcome*.

Published online: March 20, 2023; **PII**: S097475591600512

Acute kidney injury (AKI), characterized by an abrupt decrease in kidney function, is associated with substantial morbidity, increased risk of mortality and higher risk of progression to chronic kidney disease (CKD) [1]. Community-acquired AKI (CA-AKI), a subset of AKI, is presence of AKI at the time of hospitalization. In AKI Global Snapshot study, 47% of AKI episodes were due to CA-AKI, of which 80% occurred in low and low to medium income countries [2]. In contrast to hospital acquired AKI (HA-AKI), which has multifactorial origin and high mortality risk, CA-AKI chiefly has single etiology, mostly preventable and associated with lower risk of mortality [3]. In view of the limited prospectively collected data on CA-AKI in children, especially from India, this study was aimed to estimate the frequency, etiology, and outcome as well as risk factors for mortality in children with CA-AKI.

METHODS

This prospective study was conducted at an urban pediatric tertiary care hospital in northern India between October, 2020 and December, 2021. All consecutive hospitalized children between 2 months to 12 years of age with minimum 24 hours of stay and at least one serum creatinine value measured at or within 24 hours of hospitalization were assessed for eligibility. Children with known CKD, serum creatinine estimation <2 times during first 7 days of hospitalization, breakthrough seizure, corrosive ingestion, elective hospitalization, readmission within 2 weeks of discharge and those referred from other centers after 48 hours of hospitalization were excluded from the study.

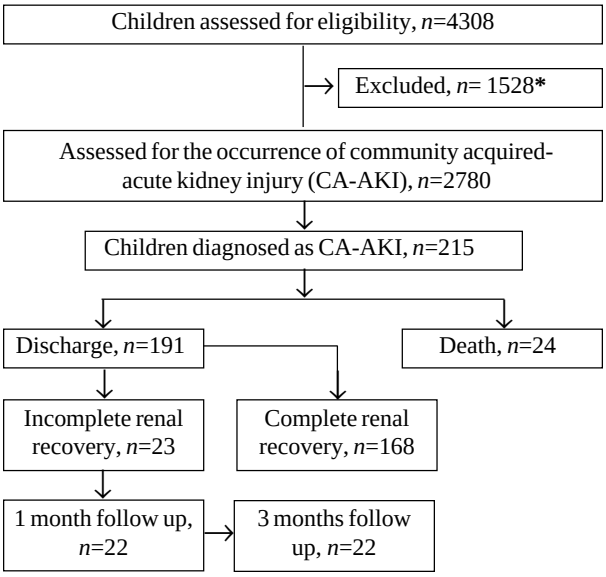
Assuming the average incidence of CA-AKI as 10% [4,5], with precision of 2% and at 95% confidence level, minimum 950 children were planned for screening, considering 10% attrition. Ethics approval was obtained from institutional ethics committee.

Invited Commentary: Pages 433-34.

Children with admission serum creatinine level of ≥1.5 times or ≥0.3 mg/dL higher than the median reference value for age [6] were presumed to have CA-AKI and enrolled for the study. A repeat serum creatinine was obtained within 24-48 hours of hospitalization. Baseline serum creatinine was defined as the lowest of any three: *i*) Serum creatinine level during last 3 months, if available; *ii*) median reference value of serum creatinine for that age; or *iii*) lowest serum creatinine value during hospitalization. Serum creatinine was estimated by modified Jaffe kinetic method traceable to IDMS using Beckman Coulter AU-680 analyzer.

Those with deranged serum creatinine level at admission were subjected to repeat blood sampling every 24-48 hours till normalization of serum creatinine value or discharge, whichever was earlier. Diagnosis and staging of CA-AKI was established by measuring subsequent fall in serum creatinine during hospitalization according to serum creatinine criterion of KDIGO classification system [7]. Final AKI stage was the maximum AKI stage achieved during hospitalization. Ultrasonography of kidney, ureter and bladder region was done where serum creatinine failed to normalize. Renal biopsy was done in cases of AKI with unknown etiology.

Outcomes were measured in terms of renal recovery at discharge, requirement of dialysis, duration of hospital stay and mortality. Renal recovery was defined as 'complete', if serum creatinine normalized to the reference range for that age, 'partial', if serum creatinine decreased to a lesser AKI stage, but still higher than the reference range and 'no recovery', if there was no change in the AKI stage. CKD was defined as eGFR <60 mL/min/1.73m^2 or eGFR >60 mL/min/1.73m^2 with structural damage or persistence of proteinuria for >3 months. Dialysis dependence was defined as persistent need of dialysis for maintaining fluid and electrolyte homeostasis. Those without complete renal recovery at discharge were further followed-up at one and three months after discharge.



**Known case of CKD/ESRD, n=24; elective hospitalization (for blood transfusion, n=165; albumin infusion, n=36; chemotherapy, n=71; IVIG infusion, n=14; pamidronate, n=21; for renal biopsy, n=36; bone marrow aspiration/biopsy, n=18; endoscopy, n=186), Breakthrough seizures, n=493; Accidental poisoning, n=87; Children with <2 serum creatinine measurement during first 7d of hospitalization, n=54; Readmission within 2 weeks after discharge, n=21; Referred from other centers after ≥48h of stay, n=302.*

Fig. 1 Study flow chart.

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24. Quantitative variables were expressed as mean or median and were analyzed by independent *t* test or Mann-Whitney *U* test, respectively. Qualitative variables were expressed as numbers/percentages and were analyzed by chi-square test or Fisher exact test. Risk factors for mortality were analyzed by logistic regression analysis.

RESULTS

Of the 4308 eligible children, 1528 were excluded and 2780 children aged 2 months to 12 years, with >24 hours of hospital stay, were assessed for CA-AKI, and 215 (7.7%, 95% CI, 6.7- 8.6) were diagnosed as CA-AKI according to KDIGO definition of AKI (**Fig. 1**).

Demographic, clinical and laboratory characteristics of children with CA-AKI are shown in **Table I**. Maximum AKI stage I, II and III were present in 11 (5%), 42 (20%) and 162 (75%) children, respectively. Diarrheal diseases with dehy-

Table I Demographic, Clinical and Laboratory Characteristics of Children With CA-AKI (*N*=215)

Characteristic	*Values*
Age group	
2-12 mo	126 (58.6)
>12 mo	89 (41.4)
Male sex	120 (55.8)
Weight (kg)[a]	7.8 (5.5,15)
Oligo-anuria	41 (19)
SBP SD score[a]	0.38 (-0.67,-0.8)
DBP SD score[a]	-0.22 (-0.8,-0.7)
Hypotension	13 (6)
PICU admission	29 (13.5)
Maximum AKI stage	
Stage I AKI	11 (5)
Stage II AKI	42 (20)
Stage III AKI	162 (75)
Dialysis	19 (9)
Peritoneal dialysis	6 (3)
Hemodialysis	13 (6)
Hemoglobin (g/dL)[b]	10.9 (3.4)
C-reactive protein (mg/L)[a]	16 (3.2,66)
Urea (mg/dL)[a]	86 (56,146)
Serum creatinine (mg/dL)[a]	
At admission	1 (0.7,1.6)
Maximum value	1.1 (0.7, 1.7)
Thrombocytopenia	42 (19.5)

Values in no. (%), [a]median (IQR) or [b]mean (SD). CA-AKI: community acquired-acute kidney injury; SBP and DBP: systolic and diastolic blood pressure; PICU: pediatric intensive care unit,

dration (*n*=85) and sepsis (*n*=61, 18 blood culture positive) were two most common causes of CA-AKI, followed by acute febrile illnesses (*n*=32) and primary renal diseases (*n*=32). Among febrile illnesses, dengue (*n*=13), pyelonephritis (*n*=5) and leptospirosis (*n*=4) were important causes of CA-AKI. Nephrotic syndrome (*n*=12) with features of hypovolemia and/or acute tubular necrosis was the most common primary renal disease associated with CA-AKI, followed by hemolytic uremic syndrome (*n*=9) and acute glomerulonephritis (*n*=10) **(Table II)**.

Out of 191 children discharged, 168 (88%) had complete renal recovery, 13 (7%) had partial renal recovery and 10 (5%) had no renal recovery. Nineteen (9%) children required dialysis (13 hemodialysis and 6 peritoneal dialysis). Median (IQR) duration of hospital stays in children with AKI stage I, II and III was 4 (3,6), 5.5 (3.7,9) and 6 (3,12.2) days, respectively. Twenty four (11%) children with CA-AKI died during hospitalization. Of 21 children who died of sepsis, 20 presented as septic shock and died even before dialysis could be started. Median SD scores of systolic and diastolic blood pressures were significantly lower in children who died in comparison to those who survived. Out of 22 children at 3 months follow-up, 10 progressed to CKD, with 3 of them becoming dialysis dependent.

On univariate analysis, sepsis, mechanical ventilation, inotropes requirement and stage III AKI were significantly associated with increased risk of mortality. On multivariate logistic regression analysis, inotropes requirement was the only independent risk factor for mortality (**Table III**).

Table II Etiological Diagnosis of Community-Acquired Acute Kidney Injury in Hospitalized Children (*N*=215)

Etiology	*No. (%)*
Diarrhea with dehydration	85 (39.5)
Sepsis	61 (28.3)
Acute febrile illnesses[a]	32 (14.9)
Dengue	13 (6.0)
Pyelonephritis	5 (2.3)
Leptospirosis	4 (1.9)
Typhoid	3 (1.4)
Primary renal diseases (*n*=32)	
Nephrotic syndrome	12 (5.6)
Hemolytic uremic syndrome	9 (4.2)
Post-infectious GN	4 (1.9)
Rapidly progressing GN[b]	6 (2.7)
Renal stones	1 (0.5)
Diabetic ketoacidosis	3 (1.4)
Dextromethorphan toxicity	1 (0.5)
MIS-C	1 (0.5)

GN: glomerulonephritis; MIS-C: multisystem inflammatory syndrome in children. [a]2 each with liver abscess, malaria and diphtheria, and 1 child with tubercular meningitis; [b]2 with lupus nephritis, and 1 each with C3 GN, anti-GBM crescentic GN, granulomatous interstitial nephritis, IgA crescentic GN.

Table III Risk Factors for Death in Children With Community-Acquired Acute Kidney Injury (*N*=215)

Variables	*OR (95% CI)*	*P value*
Requirement of inotropes	363 (26-5084)	<0.001
Sepsis	2.4 (0.4-14)	0.30
Stage III acute kidney injury	4.3 (0.16-118)	0.38
Mechanical ventilation	0.1 (0.01-1.1)	0.06

DISCUSSION

In this prospective study frequency of CA-AKI in hospitalized children was 7.7% (95% CI 6.7-8.6), with majority being in AKI stage III. Diarrheal diseases with dehydration and sepsis were predominant causes of CA-AKI. More than three fourth of cases had complete renal recovery at discharge, whereas 11% died during hospitalization. Requirement of inotropes was the only independent risk factor for mortality. Nearly half of those with incomplete renal recovery at discharge progressed to CKD at 3 months follow-up.

Frequency of CA-AKI in our study was similar to earlier studies across the globe, with incidence of CA-AKI varying between 7 to 14% [4,5,8,9]. In a meta-analysis to estimate the worldwide incidence of AKI, pooled incidence rate of CA-AKI was 8.3% [10]. Three fourth of the children in our study achieved maximum AKI stage III, similar to study by Esezobar, et al. [11], where 70% children were in 'failure' category. Majority of cases in AKI stage III in our study can be explained by predominantly infant population, which are more susceptible to infection-related AKI.

One fourth of all AKI cases in our study resulted from sepsis, similar to study from a sub-Saharan African country, where sepsis accounted for 25.7% of all AKI cases [11]. Etiological spectrum of AKI in our study was similar to other Indian studies [12,13], with infections accounting for more than half of all cases, followed by primary renal diseases.

Despite majority of our AKI cases in stage III, only 9% received dialysis, in contrast to 14.5% children requiring dialysis in a study from southern India [12]. Fewer children receiving dialysis in our study can be explained by many presenting as septic shock and succumbing within 24 hours of hospitalization even before dialysis could have been started. Mortality rate of 11% in our study was similar to pooled AKI-associated mortality rate of 13.8% in children [10]. A higher in-hospital mortality in two other Indian studies [12,13] and studies from sub-Saharan African countries [4,5] in comparison to our study can be explained by inclusion of hospital-acquired AKI cases also in their studies.

WHAT THIS STUDY ADDS?

- Majority of community-acquired acute kidney injury in hospitalized children resulted from diarrheal diseases and sepsis.

In consonance with two Indian studies [12,13], more than two-third of children in our study achieved complete renal recovery at discharge. Out of those with incomplete renal recovery, nearly half progressed to CKD at 3 months follow-up. Though, risk factors for progression to CKD were not analyzed, approximately two-thirds of surviving children who had received dialysis progressed to CKD at 3 months. In contrast to 22-35% of all AKI cases progressing to CKD at 3 months [14,15], only 5% of surviving children in our study progressed to CKD, which can be explained by majority of AKI cases due to diarrhea and fewer children requiring dialysis.

Strength of this study is prospective enrollment of cases throughout the year to include all probable CA-AKI cases with seasonal variation along with 3 months follow-up after discharge. However, the study had some limitations viz., being a single center study, results are not generalizable; urine output criterion was not used for defining AKI*;* CA-AKI in CKD cases were not assessed because of prior exclusion of known CKD cases; study not powered to assess the predictors of mortality and follow-up for children with incomplete renal recovery only, based on deranged serum creatinine at discharge, which could have missed some children showing normal creatinine but persistent proteinuria or hypertension.

To conclude, CA-AKI is common in hospitalized children, with majority resulting from diarrheal diseases and sepsis. Long-term follow-up is required in cases with incomplete renal recovery, especially those requiring dialysis because of high risk of progression to CKD.

Ethics clearance: Institutional Ethics Committee, CNBC; No F.1/IEC/CNBC/11/07/2020/78/9671, dated Sep 29, 2020.
Contributors: MK: conceptualized the study. AA: enrolled the patients, collected data, involved in patient management and prepared the initial draft; MK, KM: performed the analysis and interpretation of data. MK, AA and KM revised the draft. All the authors approved the final version of the manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394:1949-64.
2. Macedo E, Cerdá J, Hingorani S, et al. Recognition and management of acute kidney injury in children: The ISN 0 by 25 Global Snapshot study. PLoS One. 2018;13: e0196586.
3. Huang L, Xue C, Kuai J, et al. Clinical characteristics and outcomes of community-acquired versus hospital-acquired acute kidney injury: A meta-analysis. Kidney Blood Press Res. 2019;44:879-96.
4. Evans RDR, Docherty M, Seeley A, et al. Incidence, etiology, and outcomes of community-acquired acute kidney injury in pediatric admissions in Malawi. Perit Dial Int. 2018;38:405-12.
5. Hanson HR, Babcock L, Byczkowski T, Goldstein SL. Describing pediatric acute kidney injury in children admitted from the emergency department. Pediatr Nephrol. 2018; 33: 1243-49.
6. Schlebusch H, Liappis N, Kalina E, Klein G. High sensitive CRP and creatinine: reference intervals from infancy to childhood. J Lab Med. 2002;26:341-6.
7. The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. Definition and classification of acute kidney injury. Kidney Int 2012;suppl 2:19-36.
8. Safdar O, Alaydarous SA, Arafsha Y, et al. Incidence and outcome of community-acquired acute kidney injury in pediatric patients seen at an emergency department: A retrospective cohort study. Pediatr Emerg Care. 2021;37: e1429-e33.
9. Ezeonwu BU, Abonyi LE, Odetunde OI, et al. Epidemiology of community-acquired acute kidney injury in children as seen in an emergency room of Tertiary Hospital in South-South Nigeria. Saudi J Kidney Dis Transpl. 2021; 32:428-36.
10. Susantitaphong P, Cruz DN, Cerda J, et al. Acute kidney injury advisory group of the American Society of Nephrology. World incidence of AKI: a metaanalysis. Clin J Am Soc Nephrol. 2013;8:1482-93.
11. Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. PLoS One. 2012;7: e51229.
12. Krishnamurthy S, Mondal N, Narayanan P, et al. Incidence and etiology of acute kidney injury in southern India. Indian J Pediatr. 2013;80:183-9.
13. Nawaz S, Afzal K. Pediatric acute kidney injury in North India: A prospective hospital-based study. Saudi J Kidney Dis Transpl. 2018;29:689-97.
14. Tresa V, Yaseen A, Lanewala AA, et al. Etiology, clinical profile and short-term outcome of acute kidney injury in children at a tertiary care pediatric nephrology center in Pakistan. Ren Fail. 2017;39:26-31.
15. Bai S, Moorani KN, Naeem B, et al. Etiology, clinical profile, and short-term outcome of children with acute kidney injury. Cureus. 2022;14:e22563.