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Spectrum of Hospital Acquired Acute Kidney Injury in Critically ill Children in a Tertiary Level Hospital

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Syed Saimul Huque,^{1*}
Afroza Begum,¹
Md. Habibur Rahman,¹
Golam Muin Uddin,¹
Ranjit Ranjan Roy,¹
Md. Abdul Mannan,²
Md. Afiqu Islam,³
Chowdhury Ali Kawser⁴

1 Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka-1000, Bangladesh.

2 Department of Neonatology, BSMMU, Shahbagh, Dhaka-1000, Bangladesh.

3 Department of Pediatric Hemato-Oncology, BSMMU, Shahbagh, Dhaka-1000, Bangladesh.

4 Department of Pediatrics, BSMMU, Shahbagh, Dhaka-1000, Bangladesh.

* Corresponding Author

Dr. Syed Saimul Huque
Associate Professor, Department of Pediatric Nephrology, BSMMU
Email: saimul264@yahoo.com
Mobile: +8801712665657

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Introduction

Acute renal failure (ARF) is classically defined as an abrupt (hours to weeks) and prolonged loss of renal function that is reversible in the majority of cases [1]. Many different definitions of ARF exist in the literature, ranging from the need for dialysis to subtle increases in serum creatinine.

Most of these definitions have not been validated in children. The International Consensus Conference on Acute Dialysis Quality Initiative (ADQI) workgroup has introduced the term acute kidney injury (AKI) instead of ARF [2,3]. The intent of the change in terms is to standardize the

Introduction: Although hospital acquired acute kidney injury (hAKI) is common and significantly increases the risk of hospital mortality, little is known about its frequency in developing countries where ICU facilities are limited. The purpose of this study was to investigate the frequency, cause, and outcome of hAKI in critically ill children in a tertiary level hospital.

Materials and Methods: In this prospective cross-sectional study, a total 36 critically ill patients with hAKI were analyzed. hAKI was diagnosed according to the AKIN criteria. The clinical data of the patients admitted to the Pediatrics and Allied Departments in this hospital from November 2014 to October 2015 were collected.

Results: A total of 3950 patients were admitted during the study period and 1103 (27.9%) were critically ill patients. Among the critically ill children, 36 (3.3%) were diagnosed with hAKI. Among different age groups, the highest incidence (5.05%) of hAKI was seen in children aged above 10 years. Sepsis was the major cause of hAKI accounting for 44.1% followed by antibiotics (27.1%), hypovolemia (13.6%), nephrotoxic agents (10.2%), and contrast agents (5.0%). Renal replacement therapy was required only in 8.3% of the cases.

Conclusions: In comparison to other studies, this study showed a low incidence of hAKI where ICU facilities are limited. Among the hospital admitted critically ill patients, a significant number of patients may develop AKI mostly due to sepsis and use of antibiotics.

Keywords: Hospital acquired AKI; Sepsis; Critically ill children; Incidence.

Running Title: AKI In Critically Ill Children In a Tertiary Level Hospital

definition and to reflect the entire spectrum of the condition. The rate of AKI diagnosis is increased by 11% every year [4,5].

Recently, the Acute Kidney Injury Network (AKIN) workgroup [6], a sub-committee of ADQI, classified AKI into three increasing severity stages (AKI stages 1 to 3) of kidney dysfunction based on the ADQI work-group's RIFLE criteria with modifications [1].

AKI is both community and hospital acquired. Although community acquired AKI is more common, recent studies suggest that the incidence of AKI in hospitalized children is also increasing which is mostly influenced by the type of hospital [7-10]. In developed countries, cardiopulmonary bypass surgery, bone marrow transplantation, nephrotoxic medications, nosocomial infections, and multiple organ failure commonly cause hospital acquired acute kidney injury (hAKI) in critically ill patients [9-12] as compared to hospitals in developing countries, like our institute, that do not offer all these treatment facilities.

Hospital acquired AKI is defined as onset of AKI in a hospitalized patient who had no evidence of AKI (reduced urine output or elevated serum creatinine) at the time of admission [13]. Due to limited resources to treat AKI and the high mortality of AKI, it is important to take strategies for prevention of hAKI to decrease its morbidity and mortality. Therefore, using the AKI diagnostic definition and staging system by AKIN [2], we determined the hospital frequency of the AKI stage, etiology, and clinical outcome of pediatric hAKI patients at a tertiary level hospital in Bangladesh, which may facilitate better management of these patients.

Materials and Methods

This cross-sectional observational study was performed prospectively at Pediatric s and Allied Departments of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from November 2014 to October 2015. All critically ill pediatric patients and neonates without clinical evidence of AKI at baseline with normal baseline serum creatinine were screened throughout their hospital stay for development of acute renal insufficiency. The first serum creatinine obtained after admission to the hospital was taken as the baseline value. All children in the neonatal intensive care unit (NICU), children on oncology treatment, children receiving any nephrotoxic drug or contrast agent, patients undergoing any

major operative procedure, and children at risk of developing AKI like those with tumor lysis syndrome, septicemia, nosocomial infections, or hypovolemia were considered as critically ill patients. Exclusion criteria were chronic kidney disease, established impaired renal function like AGN, HUS, obstructive uropathy, and community acquired acute kidney injury like gastroenteritis, vomiting, wasp bite, etc.

After identification of critically ill children, the diagnosis of AKI was confirmed based on (1) history, (2) physical examination, (3) measurement of urine output and (4) serum creatinine. Then, AKI was staged using the creatinine criteria of the AKIN work group [2]: stage 1 AKI (AKI-1): rise in serum creatinine by ≥ 0.3 mg/dL ($26.4 \mu\text{mol/L}$) or an increase of >150 – 200% (1.5 – 2 -fold increase) from baseline; stage 2 AKI (AKI-2): rise in serum creatinine by >200 – 300% (>2 – 3 -fold increase) from baseline; and Stage 3 AKI (AKI-3): rise in serum creatinine by $>300\%$ (>3 -fold) from baseline or serum creatinine ≥ 4.0 mg/dL ($\geq 354 \mu\text{mol/L}$). At the same time, AKI patients were categorized to non-oliguric and oliguric groups. Non-oliguric AKI was defined as urine output persistently >0.5 mL/kg/h in the setting of an abnormal serum creatinine level. All these patients were followed daily until discharge, death or return of renal function to the baseline level. A serial record of urine output and serum creatinine was maintained. Hemodialysis or peritoneal dialysis was performed according to standard clinical indications. The effect of factors such as the presence or absence of oliguria, serum creatinine at the time of admission, patient's age, severity of renal insufficiency, and prognosis of acute renal failure was analyzed.

Statistical analysis was performed using unpaired Student's t test, χ^2 analysis with Yates' correction, and analysis of variance. P values less than 0.05 were considered significant.

Results

A total of 3950 patients were admitted to Bangabandhu Sheikh Mujib Medical University during the study period and 1103(27.9%) critically ill patients who met the inclusion criteria were enrolled in this study. Thirty-six children were diagnosed with hAKI according to the AKIN criteria (changes of serum creatinine and urine out-put). The distribution of Critically Ill Patients (CIP) and hospital acquired Acute Kidney Injury (hAKI) in different departments is illustrated in Table 1.

Table 1. Distribution of Critically Ill Patients (CIP) and hospital acquired Acute Kidney Injury (hAKI) in different departments

Department	Total patients	CIP (%)	hAKI (%)
General Pediatrics	971	88 (9.1)	5 (5.7)
Pediatric Gastroenterology	801	123 (15.4)	4 (3.3)
Neonatology	523	523 (100.0)	7 (1.3)
Pediatric Hemato-Oncology	722	211 (29.2)	12 (5.7)
Pediatric Nephrology	390	94 (24.1)	5 (5.3)
Pediatric Surgery	543	64 (11.8)	3 (4.7)
Total	3950	1103 (27.9)	36 (3.3)

* Numbers in parentheses are percentages

The 36 critically ill patients with hAKI were categorized into 3 age groups (<1 year, 1-10 year and >10 years). Of these 36 hAKI patients, 13 patients were in the age group <1 year, 13 were in the age group 1-10 years, and 10 were in the age group >10 years. We noted that the incidence was higher in older patients. The highest incidence (5.05%) was seen in the age group > 10 years. The overall incidence of hAKI in critically ill patients was 3.3%. Table 2 & 3 show the demographic characteristics and age-related incidence of hAKI in the critically ill patients.

Table 2. Demographic characteristics of critically ill children with hAKI in different age groups

Parameters	Age < 1 yr	Age 1-10 yr	Age > 10 yr	p value
Patients	13 (36.1)	13 (36.1)	10 (27.8)	
Sex ratio	2.25:1	1.60:1	0.42:1	
S. Creatinine				
On admission	0.47 ± 0.23	0.48 ± 0.13	0.60 ± 0.15	0.196
On AKI	2.03 ± 0.96	1.51 ± 0.97	1.76 ± 0.65	0.341
Urine output				0.407
Oliguria	6 (46.2)	4 (30.8)	2 (20.0)	
Non-oliguria	7 (53.8)	9 (69.2)	8 (80.0)	
Management				
Conservative	11 (84.6)	12 (92.3)	10 (100.0)	
PD	2 (15.4)	0 (0.0)	0 (0.0)	
HD	0 (0.0)	1 (7.7)	0 (0.0)	
eGFR (ml/min/1.73 m²)	14.3 ± 10.8	47.5 ± 18.7	48.2 ± 14.1	0.001

Table 3. Age related incidence of hAKI in critically ill patients

Age	Critically ill patients	hAKI	Incidence
< 1 year	633	13	2.05%
1 - 10 years	272	13	4.78%
> 10 years	198	10	5.05%
Total	1103	36	3.26%

ANOVA test was done to measure the level of significance.

The main causes of the hAKI in CIP were sepsis, antibiotics, hypovolemia, nephrotoxic agents, and contrast agents (Table 4). Overall, sepsis was the major cause of hAKI, accounting for 44.1% of the cases, followed by antibiotics (27.1%).

Table 4. Etiologic factors of hAKI

Factors	Frequency (n)	Percentage (%)
Sepsis	26	44.1
Antibiotics	16	27.1
Hypovolaemia	8	13.6
Nephrotoxic agents	6	10.2
Contrast agents	3	5.0

Multiple responses

Table 5 shows hospital acquired AKI according to AKIN criteria. There was no significant difference in AKIN criteria between different age groups. Failure was highest in the age group <1 year whereas injury and risk were highest in the age group 1-10 years.

Table 5. Hospital acquired AKI according to RIFLE criteria

RIFLE criteria	Age < 1 yr	Age 1-10 yr	Age > 10 yr	p value
Failure	9 (69.2)	4 (30.8)	4 (40.0)	
Injury	3 (23.1)	7 (53.8)	5 (50.0)	
Risk	1 (7.7)	2 (15.4)	1 (10.0)	
Total	13 (100.0)	13 (100.0)	10 (100.0)	0.372

Chi-square test was done to measure the level of significance.

Figure 1 shows bar diagram of serum creatinine after AKI in different departments.

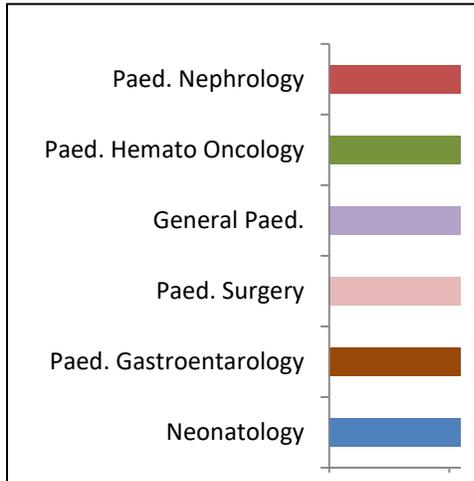


Figure 1. Bar diagram showing serum creatinine of patients after AKI in different departments

The highest mean serum creatinine was seen the Neonatology Department followed by Pediatric Nephrology (2.00 mg/dl), General Pediatrics (1.75 mg/dl), Pediatric Surgery (1.72 mg/dl), Pediatric Hemato-Oncology (1.60 mg/dl), and Pediatric Gastroenterology (1.13 mg/dl) departments. However, there was no significant difference in the clinical outcome between different creatinine levels and between oliguric and non-oliguric patients (Table 6 and Table 7).

Table 6. Clinical outcome according to different serum creatinine levels

Clinical outcome	S. Creatinine (after AKI)		p value
	<2.0 mg/dl	≥2.0 mg/dl	
Good	22 (88.0)	8 (72.7)	
Death	1 (4.0)	3 (27.3)	
No improvement	2 (8.0)	0 (0.0)	
Total	25 (100.0)	11 (100.0)	0.090

Chi-square test was done to measure the level of significance

The mean platelet count, potassium, serum creatinine, and chloride were higher in oliguric

Table 7. Clinical outcome according to oliguric and non-oliguric AKI

Clinical outcome	Oliguric	Non Oliguric	p value
Good	11 (91.7)	19 (79.2)	
Death	1 (8.3)	3 (12.5)	
No improvement	0 (0.0)	2 (8.3)	
Total	12 (100.0)	24 (100.0)	0.529

Chi-square test was done to measure the level of significance.

versus non-oliguric AKI but the difference was not statistically significant. The mean albumin, eGFR, urea, and TCO₂ were higher in non-oliguric versus oliguric AKI but the difference was not statistically significant, either.

Table 8. Biochemical parameters according to oliguric and non-oliguric AKI

Parameter	Oliguric	Non-Oliguric	p value
Platelet	376070 ± 214143	315086 ± 255636	0.515
Sodium	136.7 ± 18.2	137.2 ± 11.4	0.965
Potassium	4.7 ± 1.3	4.2 ± 1.0	0.222
Albumin	25.8 ± 5.1	26.2 ± 6.1	0.879
S. Creatinine	1.9 ± 1.1	1.6 ± 0.8	0.410
eGFR	25.2 ± 16.7	39.6 ± 23.0	0.076
Urea	68.0 ± 40.8	133.4 ± 78.8	0.101
TCO₂	22.4 ± 5.4	27.1 ± 5.3	0.098
Chloride	109.2 ± 15.9	99.8 ± 5.6	0.067

Unpaired t test was done to measure the level of significance

Discussion

The Department of Pediatric Nephrology of Bangabandhu Sheikh Mujib Medical University is a major tertiary level hospital in Bangladesh, where all severe and complicated cases from different parts of the country are referred to. There has been an increase in hospital acquired acute kidney injury in recent years [14-22]. We presume that in BSMMU, it may be attributable to the development of different subspecialties in this center, which leads to reduced mortality but can increase the morbidity. The main objective of this prospective study was to evaluate hospital-acquired acute

kidney injury considering its causative factors, clinical course, and impact on patient management. The pattern of community-acquired acute kidney injury is significantly different in third world countries as compared to economically advanced countries. In this study, 36 cases of hospital acquired AKI were identified in critically ill children and the incidence of hAKI was 3.3%. Different studies have reported different incidence rates [23-25]. Hou et al. [26] reported an incidence of 4.9% for hospital-acquired renal failure in patients admitted to the Tufts New England Medical Center in Boston and Schusterman et al. [27] reported that 2% of the patients developed this complication in the University of Pennsylvania Hospital in the USA. There are two possible reasons for this discrepancy in the reported incidence between the three studies. The definition of hospital-acquired acute renal failure used by Hou et al. [26] was rather liberal and could have included instances of laboratory or spontaneous variations accounting for changes in serum creatinine in some patients. Schusterman et al. [27] looked at this problem only in patients admitted to the medical, surgical and gynecological services. The hospital admissions in the present study included those in Pediatrics and Allied Departments where the likelihood of developing acute kidney injury is low. Therefore, we believe that the incidence of renal failure in our study is a more accurate reflection of the overall magnitude of this problem in critically ill hospitalized patients. However, those published data included all age groups, but not specifically the pediatric patients. In 2007, Bailey et al. [12] performed a prospective study in 985 PICU patients. The incidence of AKI of these PICU patients was 4.5%, which is higher than our incidence. They defined AKI as doubling of serum creatinine and included both community acquired as well as hospital acquired AKI cases.

In this study, sepsis was the foremost cause of AKI according to multiple responses. Hypovolemia, antibiotics, nephrotoxic agents, and contrast agents sometimes cause AKI in critically ill patients. Nephrotoxic AKI is commonly associated with aminoglycoside administration [7]. In our study, along with aminoglycosides, other antibiotics like meropenem, ceftazidime, vancomycin, and ciprofloxacin induced AKI, as well. Among antihypertensive drugs, ACE inhibitors were the main cause of AKI in our setting. Therefore, physicians need to know about the renal function of the critically ill patients before using antibiotics and other nephrotoxic

drugs. In centers where cardiac surgery and stem cell transplantations are available, surgical treatment of congenital heart disease and stem cell transplantations are major causes of death because of hypoxia and poor perfusion leading to multi organ failure [28]. In a study in neonates, the incidence of AKI ranged from 8% to 24% of newborns and AKI was particularly common in neonates who underwent cardiac surgery [16,9]. Our study did not include these patients.

Hypovolemia was the third most common cause of hAKI in our study. The causes of hypovolemia included gastroenteritis and inadequate fluid therapy for patients who presented with other problems in different departments. Fortunately, early detection and proper management in our institution produced favourable outcomes in such cases. Eight cases were diagnosed with hAKI due to hypovolaemia. Their prognosis was good and they did not require dialysis.

Currently, there is not a uniform definition of AKI in adult and pediatric patients, and AKI is defined in multiple ways, but the majority of AKI definitions currently in use involve a change in the serum creatinine level. A new classification system entitled the RIFLE criteria (R: risk for renal dysfunction, I: injury to the kidney, F: failure of kidney function, L: loss of kidney function, and E: end-stage renal disease) has been proposed as a standardized classification of acute kidney injury in adults [3] and has been adapted for pediatric patients [29]. The pediatric RIFLE (pRIFLE) classifies pediatric AKI better and reflects the course of AKI in children admitted to the intensive care unit (ICU) [29]. In this study, the AKIN criteria were applied to compare its validity and utility in different age groups. The increase in the mean serum creatinine level ≥ 2 mg/dl was mainly seen in critically ill patients admitted to the Neonatology and Pediatric Nephrology Department. Therefore, patients in other departments are less likely to develop renal failure. This again is possibly explained by the more stringent criteria used for the diagnosis of acute kidney injury in the present study. Although some studies [30] have shown that oliguria is associated with higher morbidity and mortality, we found a higher rate of morbidity and mortality in non-oliguric patients. Multi organ system failure and increased use of diuretics could increase morbidity and mortality in non-oliguric patients.

Normally, dialysis is the last modality of treatment for AKI cases with volume overload or metabolic disturbances. Supportive treatment usually plays

the most important role. Therefore, patients who undergo dialysis are likely to have severe AKI, and the mortality rate would be expected to be higher in this group. This does not mean that renal replacement therapy (RRT) is a poor procedure but that RRT is a rescue procedure when renal failure occurs; RRT is the most important procedure for bridging the time needed for recovery. In this study, most of the patients were managed conservatively (91.7%). Dialysis was required in only three cases.

The best way to avoid hospital acquired acute kidney injury is prevention, followed by early detection, conservative treatment, and referral to an institution where RRT is available. However, multiple organs involvement also affects the outcome if these problems are not resolved [31]. Mortality rates are very high, even with RRT, if three organs fail [32]. It is anticipated that RRT and ICU care will continue to advance, which should improve the outcome of AKI cases, but we must consider the fact that congenital heart disease surgery and oncologic treatments are also advancing, which will increase the number of cases and complications. AKI related to other systemic diseases occurs more frequently than AKI secondary to primary renal disease; therefore, advances in treating the condition, with reductions in mortality rates, may well be offset by an increased number of cases resulting from secondary causes.

Conclusions

In this study, the incidence of hAKI was 3.3% where ICU facilities are limited. Our results showed that the most frequent cause of AKI in hospitalized patients was sepsis. Despite a major difference in the spectrum of etiologies and outcomes of oliguric and non-oliguric acute kidney injury between this study and other studies, the pattern of hospital-acquired acute kidney injury is nearly identical. Active treatment of primary diseases, avoidance of complications, and use of supportive treatment are beneficial in improving the prognosis of the critically ill patients with AKI.

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Conflict of Interest

None

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