

Clinical characteristics and mortality risk prediction in children with acute kidney injury

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ABSTRACT

Background: Acute kidney injury (AKI) is characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately. **Objective:** AKI is a serious condition in critically ill patients. The aim of the study was to determine incidence rate, identify risk factors, and describe the clinical outcome of AKI in the Pediatric Intensive Care Unit (PICU). **Materials and Methods:** This prospective observational study was conducted in the PICU of a hospital in the South-east Area of Iran (Zahedan City), to study the clinico-etiological profile of AKI (defined according to the AKI network criteria). Over a period of 20 months from April 2012 to December 2014, 303 children were included in the study. Both the groups of patients, those who developed AKI and those who did not develop AKI, were then followed during the course of their hospital stay. **Results:** There were 303 cases included in the study, with the incidence rate of AKI of 14.9% in PICU. The most common PICU admission diagnoses in AKI were neurologic 85 (%28.05), followed by heart diseases 52 (17.18%) and 31 (10.23%) for respiratory diseases. AKI was 43.5 and 5.4 times more prevalent in renal and endocrine patients compared to those with heart disease respectively. The mortality rate was estimated to be higher in patients with AKI compared to their counterparts (40% vs. 17.8%). Chance of death increased in patients with AKI (odds ratio = 3.04). **Conclusion:** AKI is a serious problem, but its true incidence is unknown. Understanding the epidemiology of AKI by using of standard definition help us to find high-risk children that are the first step to improve outcomes. The future multiple-center study may benefit by better identifying risk factors and early detection of AKI by using biomarkers novel to prevent the developing of AKI.

Key words: Acute kidney injury, children, Pediatric Intensive Care Unit

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INTRODUCTION

Acute kidney injury (AKI) is characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately.^{1,2} The incidence of acute renal failure (ARF) varies according to the population in the study and the definition of ARF employed. Approximately 5-12% of children who hospitalized in Intensive Care Unit (ICU) have different degrees of AKI.^{3,4} Mortality rates are high in critically ill children with AKI, ranging between 9%

and 67%.⁵ Recent reviews emphasize that disparities in the definition of AKI have resulted in large variations in reported incidence and outcomes.² The AKI network (AKIN) workgroup, a subcommittee of Acute Dialysis Quality Initiative (ADQI), recently classified AKI into three increasing severity stages (AKI Stages 1-3) of kidney dysfunction based on the ADQI work-group's RIFLE criteria with modifications. The acronym RIFLE refers to risk (AKI

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Stage 1), injury (AKI Stage 2), failure (AKI Stage 3), and loss of kidney function and end-stage renal disease (ESRD).² This serious disorder has the potential for progression to irreversible loss of kidney function or ESRD. Progression may be rapid and severe in those with preexisting kidney disease. From pediatric patients who had AKI 40-50% showed a sign of chronic renal insufficiency.⁵ AKI can be divided in terms of prerenal injury, intrinsic renal disease, including vascular insults, and obstructive uropathies. The history, physical examination, and laboratory tests such as urinalysis and radiographic studies can establish the likely cause(s) of AKI. In many instances, such as AKI occurring in hospitalized children, multiple factors are likely to be implicated in the etiology. The epidemiology of AKI is quite different in developed and developing countries. In developed countries, AKI was more common in ICUs.^{1,6} The prognosis of AKI is highly dependent on AKI etiology. Children who have AKI as a component of multisystem failure have a much higher mortality rate than children with an intrinsic renal disease such as hemolytic uremic syndrome, rapidly progressive glomerulonephritis, and acute interstitial nephritis. Recovery from intrinsic renal disease is also highly dependent on the underlying etiology of the AKI.⁷ Changes in management strategy of fluid therapy and infection control can result in a dramatic reduction in the incidence and severity of AKI.² Because of high costs of renal replacement therapies (RRTs) in developing countries, prevention still is the only realistic way to decrease severe impacts on morbidity and mortality. Early detection and appropriate treatment can provide complete recovery. The objective of this study was to review the prevalence, cause, and mortality rate of AKI in.

MATERIALS AND METHODS

This prospective observational study was conducted in a general hospital belongs to the Zahedan University of Medical Sciences in the South-east Area of Iran, over a period of 20 months from April 2012 to December 2014. We enrolled critically ill patients admitted to the Pediatric Intensive Care Units (PICUs) for at least one night aged from 1-month to 15 years. We determined the incidence of AKI as defined by the AKIN classification and were studied the etiology and short-term outcome of AKI in critically ill children and compared the demographic and clinical parameters among the groups. The patients divided into two groups, including patients who developed AKI and nondeveloped. They followed during the course of their hospital stay. AKI was diagnosed based on the AKIN criteria as an absolute increase in serum creatinine (SCr) level within 48 h of bilateral kidney insult by ≥ 0.3 mg/dl or a 50% (1.5-fold) increase in SCr or more from the baseline. AKI was staged using the creatinine criteria of the AKIN work-groups.² Stage 1 AKI (AKI-1): Rise in SCr by ≥ 0.3 mg/dl or an increase of >150 – 200% (1.5-2-fold increase) from baseline; Stage 2 AKI (AKI-2): Rise in SCr by >200 – 300%

(>2 – 3 -fold increase) from baseline; Stage 3 AKI (AKI-3): Rise in SCr by $>300\%$ (>3 -fold) from baseline or SCr ≥ 4.0 mg/dl with an acute rise of at least 0.5 mg/dl.² The study was approved by the Institutional Ethics Committee. Informed consent was obtained from the parents prior to the inclusion of subjects into the study. We estimated base SCr by using average norms in all patients. The inclusion criteria were hospitalized children and adolescents without clinical evidence of AKI at baseline, with normal baseline SCr or epidermal growth factor receptor but who later developed AKI following either therapeutic intervention, nosocomial infection or any other severe clinical conditions. Patients with known chronic kidney disease, abnormal baseline SCr, and/or diminished urine output at baseline were excluded. The cases were classified in the following 3 age groups: Infant (1-month to 1-year), toddlers (>1 -year to 5 years), and children (>5 years). At the admitted time, all subjects were measured SCr. For the estimation of SCr, the Modified Jaffe method was used with autoanalyzer. This value was considered as “initial” SCr. Estimation of SCr was daily repeated until discharge from the hospital. An absolute increase in SCr of ≥ 0.3 mg/dl or an increase in SCr of more than or equal to 1.5-fold from the initial SCr was considered as AKI. Although AKI was staged at the time of diagnosis, the maximum SCr (maxSCr) level reached in each patient was used for the final AKI staging. The maxSCr was defined as the highest SCr level reached in any patient either before death or before a gradual return to normal in survivors. Indications for RRT were as per standard hospital protocols. The provisional diagnosis at admission and final diagnosis (at discharge or death) were recorded. The cause of AKI was defined as the major underlying disease. Demographic parameters and short-term outcomes (complete renal recovery, partial renal recovery, and death) were recorded. Patients were followed up until discharge. Complete renal recovery was defined as normal SCr for age (0.2–0.4 mg/dl for infants, 0.3–0.7 mg/dl for 1–12 years, 0.5–1 mg/dl for >12 years) and normal blood pressure at discharge. Partial renal recovery was defined as elevated SCr for age or persistent hypertension at discharge. The study was approved by the Institutional Ethics Committee. Informed consent was obtained from the parents prior to the inclusion of subjects into the study. Measurements were summarized as a mean \pm standard deviation and percentages for continuous and categorical variables. Data were analyzed using univariate and multivariate logistic regression models in SPSS for Windows, Version 16 (SPSS Inc., Chicago).

RESULTS

In this study, 303 eligible patients were investigated. Of all, 58.4% were male and mean age was 2.96 ± 3.76 so that 55.1% were <1 -year old. The most common etiologies were neurologic (28.1%) and heart (17.2%) diseases. Out of all patients, 56.5% had metabolic acidosis while 21.8% and 20.2% had Na and K abnormalities, respectively.

Forty-five children had AKI giving an incidence of 14.9%. Of all AKI patients, 35.7%, 9.5%, and 54.8% were in Stages 1, 2, and 3, respectively. Furthermore, 26 (57.8%), 5 (11.1%), and 14 (31.1%) were pre- and post-renal diseases, respectively. A total of 27 patients with AKI had a complete recovery, and 8 children required dialysis. The mean of maximum creatinine values was 2.14 ± 1.87 mg/dl during the hospitalization. There was no association between age, gender, season, metabolic acidosis, and the level of Na and K with AKI. However, AKI was 43.56 and 5.4 times more prevalent in renal and endocrine patients compared to those with heart disease, respectively [Table 1]. Of all patients, 64 (21.1%) cases died in the hospital. Death in patients with acute renal injury (40%) was significantly more than others (17.8%) so that chance of death increased in patients with AKI (odds ratio [OR] = 3.04). Similarly, patients with abnormal Na had 3.1 times more chance of death. Although malignancy and sepsis were related to death in univariate analysis, no association was detected in multivariate analysis [Table 2].

DISCUSSION

This study described AKI in a unselected group of children admitted to PICU ward in a hospital of Zahedan City, Iran. Two recently classification, the RIFLE and AKLN criteria have been validated as diagnostic and prognostic tools in critically ill children patients with AKI.^{8,9} Using the methods show that incidence of AKI varied from 8.2%¹⁰ to 82.9%.¹¹ In this study, the prevalence of AKI defined using AKI definition based on the acute kidney network staging system, was 14.9%. In a retrospective cohort study in Montreal, QC, Canada, 17.9% of children admitted to two PICU developed AKI that was same as our study. The rising prevalence's of AKI has been documented in both developed and developing countries such as Nigeria,¹¹ North India³, which were 82.9% and 36.1%, respectively. This may partly be due to the definitions of AKI becoming more sensitive and may reflect an increase in detection rather than an overall increase in the incidence of disease [Table 3].

Table 1: OR of factors potentially related to AKI

Factor	Total number (%)	AKI number (%)	Univariate analysis Unadjusted OR* (95% CI*)	Multivariate analysis Adjusted OR* (95% CI*)
Age (year)				
≤1	167 (55.1)	25 (15.0)	1.0	
1-5	72 (23.8)	6 (8.3)	0.52 (0.20, 1.32)	
>5	64 (21.1)	14 (21.9)	1.59 (0.77, 3.30)	
Gender				
Male	177 (58.4)	25 (14.1)	1.0	
Female	126 (41.6)	20 (15.9)	1.15 (0.61, 2.17)	
Season				
Spring	61 (20.1)	9 (14.8)	0.79 (0.27, 2.33)	
Summer	143 (47.2)	18 (12.6)	0.66 (0.25, 1.71)	
Fall	60 (19.8)	11 (18.3)	1.03 (0.36, 2.92)	
Winter	39 (12.9)	7 (17.9)	1.0	
Disease				
Heart	52 (17.2)	3 (5.8)	1.0	1.0
Malignancy	27 (8.9)	3 (11.1)	2.04 (0.38, 10.88)	2.04 (0.38, 10.88)
Neurologic	85 (28.1)	11 (12.9)	2.43 (0.64, 9.15)	2.46 (0.65, 9.28)
Renal	12 (4.0)	9 (75.0)	49.00 (8.51, 282.27)*	43.56 (7.45, 254.75)*
Sepsis	24 (7.9)	5 (20.8)	4.30 (0.93, 19.78)	4.30 (0.93, 19.78)
Endocrine	17 (5.6)	4 (23.5)	5.03 (0.99, 25.32)	5.44 (1.07, 27.64)*
Respiratory	31 (10.2)	4 (12.9)	2.42 (0.50, 11.62)	2.42 (0.50, 11.62)
GI	25 (8.3)	5 (20.0)	4.08 (0.89, 18.72)	4.54 (0.98, 20.95)
Others	30 (9.9)	1 (3.3)	0.56 (0.06, 5.67)	0.58 (0.06, 5.88)
HOC ₃				
Metabolic acidosis	169 (56.5)	27 (16.0)	1.26 (0.66, 2.43)	
Normal	130 (43.5)	17 (13.1)	1.0	
Na				
Hyponatremia	65 (21.5)	14 (21.5)	1.82 (0.90, 3.68)	
Normal	237 (78.2)	31 (13.1)	1.0	
Hypernatremia	1 (0.3)	0 (0.0)	—	
K				
Hypokalemia	52 (17.2)	7 (13.5)	1.0	
Normal	241 (79.8)	36 (14.9)	1.13 (0.47, 2.70)	
Hyperkalemia	9 (3.0)	2 (2.2)	1.84 (0.32, 10.69)	

*Significant result. *OR – Odds ratio; *CI – Confidence interval. AKI – Acute kidney injury

Table 2: OR of factors potentially related to death

Factor	Total number (%)	Death number (%)	Univariate analysis OR* (95% CI*)	Multivariate analysis OR* (95% CI*)
Age (year)				
≤1	167 (55.1)	37 (22.2)	1.0	
1-5	72 (23.8)	13 (18.1)	0.77 (0.38, 1.56)	
>5	64 (21.1)	14 (21.9)	0.98 (0.49, 1.97)	
Gender				
Male	177 (58.4)	37 (20.9)	1.0	
Female	126 (41.6)	27 (21.4)	1.03 (0.59, 1.81)	
Season				
Spring	61 (20.1)	13 (21.3)	1.0	
Summer	143 (47.2)	30 (21.0)	0.98 (0.47, 2.04)	
Fall	60 (19.8)	11 (18.3)	0.83 (0.34, 2.03)	
Winter	39 (12.9)	10 (25.6)	1.27 (0.50, 3.27)	
Disease				
Heart	52 (17.2)	5 (9.6)	1.0	
Malignancy	27 (8.9)	10 (37.0)	5.53 (1.65, 18.51)*	
Neurologic	85 (28.1)	19 (22.4)	2.71 (0.94, 7.76)	
Renal	12 (4.0)	2 (16.7)	1.88 (0.32, 11.11)	
Sepsis	24 (7.9)	8 (33.3)	4.70 (1.34, 16.46)*	
Endocrine	17 (5.6)	3 (17.6)	2.01 (0.43, 9.50)	
Respiratory	31 (10.2)	4 (12.9)	1.39 (0.34, 5.63)	
GI	25 (8.3)	6 (24.0)	2.97 (0.81, 10.90)	
Others	30 (9.9)	7 (23.3)	2.86 (0.82, 10.00)	
HOC ₃				
Abnormal	192 (64.2)	42 (21.9)	1.08 (0.61, 1.93)	
Normal	107 (35.8)	22 (20.6)	1.0	
Na				
Abnormal	66 (21.8)	26 (39.4)	3.40 (1.86, 6.22)*	3.10 (1.66, 5.79)*
Normal	237 (78.2)	38 (16.0)	1.0	1.0
AKI				
No	258 (85.1)	46 (17.8)	1.0	1.0
Yes	45 (14.9)	18 (40.0)	3.07 (1.56, 6.04)*	3.04 (1.50, 6.15)*
K				
Hypokalemia	52 (17.2)	9 (17.3)	1.0	
Normal	241 (79.8)	51 (21.2)	1.28 (0.59, 2.80)	
Hyperkalemia	9 (3.0)	3 (33.3)	2.39 (0.50, 11.38)	

*OR – Odds ratio; *CI – Confidence interval; AKI – Acute kidney injury; *Significant at the level of $p < 0.05$

Table 3: Summary of some reports describing the incidence of AKI

Author (references)	Number of subject	AKI definition used	AKI incidence (%)	Mortality (%)
Mehta <i>et al.</i> , 2012 ³	73	AKIN	36.1	37
Vachvanichsanong <i>et al.</i> , 2006 ¹⁰	318	AKIN	8.2	41.5
Krishnamurthy <i>et al.</i> , 2013 ²²	215	AKIN	25.1	46.3
Martin <i>et al.</i> , 2013 ⁴	1496	RIFLE	4.4	40
Shaheen <i>et al.</i> , 2006 ²³	83	RIFLE	45	20
Olowu <i>et al.</i> , 2012 ⁷	3286	AKIN	31.3	28
Bailey <i>et al.</i> , 2007 ¹⁴	985	AKIN	4.5	29.6
Otukesh <i>et al.</i> , 2006 ¹⁵	300	RIFLE	38	29.7

AKIN – Acute kidney injury network; AKI – Acute kidney injury; RIFLE – Renal failure

In our study, the most common factor for AKI was renal and endocrine diseases so that at the time of admission

AKI was 43.5% and 5.4% times more than the prevalence in the compared to the patients with heart disease in reference, respectively. Many risk factors have been defined for developing of AKI are hypovolemia,¹⁰ hypotension,¹⁴ sepsis,^{10,15,16} preexisting renal diseases,¹⁰ coagulopathy,¹⁴ and heart disease.^{14,17} Cause of AKI is frequently categorized as prerenal, renal, and postrenal. In our patients did so and, therefore, prerenal causes were common than the others, but many causes of AKI likely represented as multifactorial etiologies. In a study in Nepal four cases with prerenal azotemia and 25 cases with acute tubular necrosis (ATN) accounting for 64% of all cases. The most common causes of AKI were gastroenteritis (22%) and sepsis (20%) in the study.¹⁶ The etiology of AKI in children varies in developed and developing countries. In developed countries, major surgeries, complication associated with malignancies, and use of nephrotoxic drugs cause AKI.³ In developing countries hemolytic uremic syndrome, severe systemic infection, gastroenteritis, and postinfectious glomerulonephritis were important cause of AKI.³ In this study, neurologic disease was the major cause of AKI, accounting for 24.4%, followed by renal disease (20%), and sepsis (11.1%). In the opposite side in compare with a previous study in Iran¹⁵ the main disease causing AKI in children have been changed. In the study done by Otukesh *et al.*, prognostic indicators of AKI included several risk factors such as sepsis, respiratory distress, and age. The most common causes were changed by time from ATN, (38%), acute glomerulonephritis (24%), and hemolytic uremic syndrome (24.1%)¹⁵ to renal and endocrine causes according to the results of our study. The causes of AKI were also different in some studies in developed and developing countries. In Thailand sepsis was the major cause (21.4%)¹⁰ in study by Chang *et al.*¹⁸ the main causes for AKI were divided into two primary (20.7%) and extra renal diseases (79.3% for sepsis, hemato-oncologic diseases, and cardiovascular). In India, AKI occurred in association with infection (55.4%), acute gastroenteritis (16.9%), cardiac disease (14.8%), and hemolytic uremic syndrome (3.6%).¹² But in our main causes were sepsis (11.11%), acute gastroenteritis (11.11%), cardiac disease (6.67%), renal diseases (20%), and neurologic (24.44%). The decline in gastroenteritis related AKI reflect the worldwide decline in diarrhea related mortality which has been partly attributed to better treatment and increase usage of the Oral rehydrate solution at home. This study has been showed two patients had malaria in which is similar to the relative contribution of malaria to AKI in Nigeria¹¹ and Nepal¹⁶ Bailey¹⁴ reported that the most common cause of ARF were hemolytic uremic syndrome (18.2%), oncologic pathology (18.2%), and cardiac surgery (11.4%). In another study, the overall incidence of AKI in ICU patients ranges from 20% to 50% with lower incidences in the elective surgical patients and higher incidence in sepsis patients.¹⁹ Ganesan *et al.* also reported the common leading diagnoses in admission were respiratory (37%), neurologic

(18%), and infectious disease (17%)²⁰ in comparison to Indian results in which were sepsis, bronchopneumonia, status epilepticus, and renal disorder as highlighted causes in patients with AKI⁹ AKI still affects high mortality, logistic regression analysis showed mortality in patients with acute renal injury (40% and OR = 3.04) was significantly more than others (17.8%). This suggests that increased mortality seen in patients with a higher stage of AKI were sicker with more organ failure. In our study, the overall mortality rate was 40% that is similar to the finding of the several studies from different parts of the world and different hospital setting.^{3,4,10,12} Hypernatremia, malignancy, and sepsis were related to death in univariate analysis. In study of Krishnamurthy *et al.* independent predictor's mortality in AKI were dysnatremia and meningoencephalitis.¹² Paudel *et al.* in a study in India reported that 93% of patients have died in AKI group whereas 53.7% patients have died in the non-AKI.²¹ Bailey also reported that the mortality rate was higher in patients with ARF compared with patients without ARF (29.6% vs. 2.3%)¹⁴ and also AKI was associated with increasing in mortality (OR = 3.7, 95% CI = 2.1-6.4) in the study of Alkandari *et al.*²² that is same to the other and our studies.^{8,21} Many studies assessed some factors that influence the incidence of mortality in these patients by multiple logistic regression analysis. They revealed, sepsis²³ and number of organ failures,^{18,23} the need of dialysis,²¹ the use of mechanical ventilation,^{9,15,21,24} and disseminated intravascular coagulation¹⁵ can be regarded as independent factors for mortality. Vachvanichsanong *et al.* was reported that the overall mortality rate was 41.5%, and logistic regression analysis showed that disease groups and creatinine levels were significant independent predictor of outcome.¹⁰ The development of AKI was an independent factor of morbidity associated with long duration of hospital stay, and with a need for long mechanical ventilation.²⁴ The present study had multiple limitations. First, this study was performed at a single and referral center for patients who were sicker and needed special treatment, and it might results in an overestimation of the incidence of AKI and its association with outcomes. Secondly, there was a lack of information on outcome after discharge as following the patient and assessing long-term renal function and morbidity was difficult.

CONCLUSION

AKI is a serious problem, but its true incidence is unknown. Understanding the epidemiology of AKI by using of standard definition help us to find high-risk children that are the first step to improve outcomes. Future study may benefit by better identifying risk factors and early detection of AKI by using biomarkers novel to prevent the developing of AKI.

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Conflicts of interest

There are no conflicts of interest.

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