ORIGINAL RESEARCH

Microalbuminuria as an early marker of acute kidney injury (AKI) in children with sepsis

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ABSTRACT

Background: Acute Kidney Injury (AKI) is on the rise among critically ill children. Sepsis is one among the common causes that predisposed to AKI. Early identification and timely intervention of AKI in sepsis children is the need of the hour to reduce the morbidity and mortality. Microalbuminuria has been shown to predict organ failure early in the course. This study intends to evaluate protein/creatinine ratio as a predictor for development of acute kidney injury in critically ill septic children. **Methodology:** A prospective observational study conducted at a tertiary care centre, Tamil Nadu over one year. AKI was defined by AKIN criteria. Baseline details were collected and serial serum creatinine levels were done. Urine spot protein creatinine ratio was done on day 2 of PICU admission and followed up for development of AKI. Statistical analyses were done using SPSS19. **Results:** A total of 93 children were included of which 54 (58.1%) were boys and 39 (41.9%) were girls. The incidence of Acute Kidney Injury among the sepsis children was 39.8%. Microalbuminuria was present in 78.4% children with AKI. The mean protein to creatinine ratio in AKI group was 39.76 ± 13.3.Protein:creatinine ratio of >30 predicted the development of AKI in sepsis children with a sensitivity of 85.4%, specificity of 88%, positive predictive value of 81.6% , negative predictive value of 87.1%and an AUC of 0.81 (95% CI 0.72 – 0.90). **Conclusion:** Urine protein:creatinine ratio may be included as a part of a routine screening tool, in children with sepsis, to risk stratify those patients who are at increased risk of AKI.

Keywords: Microalbuminuria, Sepsis, Acute Kidney Injury

INTRODUCTION

Acute kidney injury (AKI) denotes sudden loss of kidney function resulting in disruption of fluid and electrolyte homeostasis. Sepsis being one of the most common predisposing factor for AKI plays a prime role in the development of kidney injury and multiple organ failure[1, 2].In children admitted with sepsis, as many as 1 in 5 may present with some degree of AKI during the course of treatment and elicit an increased rate of mortality[3]. Though many reasons have been quoted for development of AKI in sepsis, tissue hypoperfusion remains the major one. This is given by the fact that resuscitation aiming to restore tissue perfusion minimizes the kidney injury[4].

Sepsis leads on to endothelial dysfunction which triggers potent inflammatory cascades releasing pro-inflammatory and anti-inflammatory molecules into the circulation[5]. Systemic capillary leak resulting due to the disruption of endothelial barrier integrity causes increased glomerular excretion of albumin in the urine[6, 7]. Microalbuminuria, therefore occurs early after severe inflammatory process and has been shown to predict organ failure[8-10]. Urinary albumin is one of the most important prognostic-predictive factors in

chronic kidney disease. We intended in our study to evaluate urine protein/creatinine ratio as a predictor for development of acute kidney injury in critically ill septic children.

Acute Kidney Injury is defined as per Acute kidney Injury Network (AKIN)[11]. AKIN proposed a new classification which relies on serum creatinine and not on GFR changes AKIN staging has been shown in table I.

AIMS AND OBJECTIVES

To predict the development of Acute Kidney Injury in critically ill sepsis children using urine protein/creatinine ratio.

METHODOLOGY

This was a prospective observational study of critically ill sepsis children admitted to Paediatric Intensive care Unit (PICU) of a tertiary care teaching hospital, Tamil Nadu, India. Children diagnosed with sepsis within the age group of 1 month to 12 years admitted in the Pediatric Intensive Care Unit with length of stay for atleast 48 hours in PICU were included in the study after getting consent from parents. The study period was 1 year. Institutional ethical committee approval was obtained. Patients with known chronic kidney disease stage 5 (estimated glomerular filtration rate < 15 ml/min/1.73 m^2), Post-operative children from surgical correction of cyanotic congenital heart disease within 90 days, Children with ICU length of stay less than 48 hours, Children with comorbidities such as hypertension, type 1 diabetes mellitus were excluded.

Baseline variables were collected including demographic information, admission diagnoses and co-morbidities, serum creatinine value was measured on the time of admission and repeated every 24 hours. A spot urine sample was taken and urine protein to creatinine ratio was measured in the morning on day 2 of PICU admission. The cut-off of urine protein to creatinine ratio used in our study was 30 (equivalent to 300 mg/day of proteinuria).

Sepsis was defined by presence of at least two of the following criteria, one of which must be abnormal temperature or leucocyte count:

- Core temperature >38.5 C (103 F) or < 36 C (96.8 F)
- Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, painful stimulus or otherwise unexplained persistent elevation over a 0.5 – 4 hour time period.

(OR)

For children <1 year, bradycardia, defined as a mean heart rate < 10thpercentile for age in the absence of external vagal stimulus, betablocker or CHD or otherwise unexplained persistent depression over a 0.5 hour time period.

- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia.
- Leucocyte count elevated or depressed for age (not secondary to chemotherapy induced leucopenia) OR >10% immature neutrophils.

Age group	Tachycardia (95th percentile)	Bradycardia (95th percentile)	Tachypnea (95th percentile)	WBC (95th& 5th percentile)	SBP (5th percentile)
1 month – 1 year	>180	<90	>34	>17500 or <5000	<75
2 – 5 year	>140	NA	>22	>15500 or <6000	<74
6 – 12 year	>130	NA	>18	>13500 or <4500	<83

(Adapted from John Hopkins Harriet Lane Handbook of paediatrics, Rudolphs paediatrics 21/e)

- Classification of AKI was based on AKIN staging as shown in table 1.
- Patients were then followed up for the development of AKI, ICU length of stay and hospital mortality, and the associations of those with initial protein to creatinine ratio were tested.

Statistical analysis were done using SPSS 19. Continuous data were reported as mean ± SD (if normally distributed) and median (range) (if non-normally distributed). Categorical variables were expressed as proportions. Continuous variables with normal distribution were compared using Student *t*-test while those not normally distributed were analyzed using Mann Whitney U test. Categorical data were analyzed using Pearson Chi-square test or Fischer exact test. P value was calculated using chi square test. Diagnostic performance of protein to creatinine ratio in predicting AKI was evaluated using receiver operating characteristic curves.

RESULTS

A total of 93 children were diagnosed to have sepsis in the Paediatric Intensive Care Unit during the study period. Our study included 54 (58.1%) boys and 39 (41.9%) girls. The incidence of Acute Kidney Injury among the sepsis children in our study was 39.8% (37 developed AKI out of 93 Cases). Out of 37 AKI cases, 21 (56.8%) were boys and 16 (43.2%) were girls. These demographic and clinical data are shown in table II.

The median age group of 93 children was 14 months (range 2 – 144 months). The median age group of those who developed AKI was 24 months (range 2-130 months). The duration of stay of the entire study population was 8.24 ± 4.05 days. The mean duration of stay in AKI children was 10.18 ± 5.22 days. Overall mortality was 36.5% (34 expired). 20 out of 37 (54.1%) who developed AKI expired. Renal Replacement Therapy was required in 11/37 (29.7%) children.

Microalbuminuria was present in 78.4% children who developed AKI. The mean protein to creatinine ratio in AKI group was 39.76 ± 13.3 and of the non AKI group was 10.44 ± 9.07. The comparison of details among AKI and non AkI children in shown in table III. Protein:creatinine ratio of >30 predicted the development of AKI in sepsis children with a sensitivity of 85.4%, specificity of 88%, positive predictive value of 81.6% and a negative predictive value of 87.1%. Our study had an AUC of 0.81 (95% CI 0.72 – 0.90) as shown in table IV and Figure I.

Table I: Definition and classification of AKI[11]

Definition:

An abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, an increase in serum creatinine of more than or equal to 1.5 fold from baseline, or a reduction in urine output (documented oliguria of less than 0.5 ml/kg/h for more than 6 hours.

Classification/Staging System for Acute Kidney Injury

Stage	Serum Creatinine criteria	Urine Output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 1.5- to 2-fold from baseline	Less than 0.5 ml/kg per hour for more than 6 h
2	Increase in serum creatinine to more than 2- to 3-fold from baseline	Less than 0.5 ml/kg per hour for more than 12 h
3	Increase in serum creatinine to more than 3-fold from baseline or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl	Less than 0.3 ml/kg per hour for 24 h or anuria for 12 h

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

TABLE II: DEMOGRAPHIC DATA AMONG AKI & Non AKI CASES

DATA	AKI	Non AKI	P value
TOTAL	37 (39.8%)	56 (60.2%)	
MALE	21 (56.8%)	33 (58.9%)	
FEMALE	16 (43.2%)	23 (41.1%)	
AGE, in median	24 months (2 – 130)	10 months (2-144)	
Length of Stay(days), mean	10.18 ± 5.22	6.4 ± 2.16	0.001
RRT	11 (29.7%)	0	
MORTALITY	20 (54.1%)	14 (25%)	
Protein:Creatinine ratio, mean	39.76 ± 13.3	10.44 ± 9.07	0.001

TABLE III: COMPARISON OF PCR IN AKI CASES

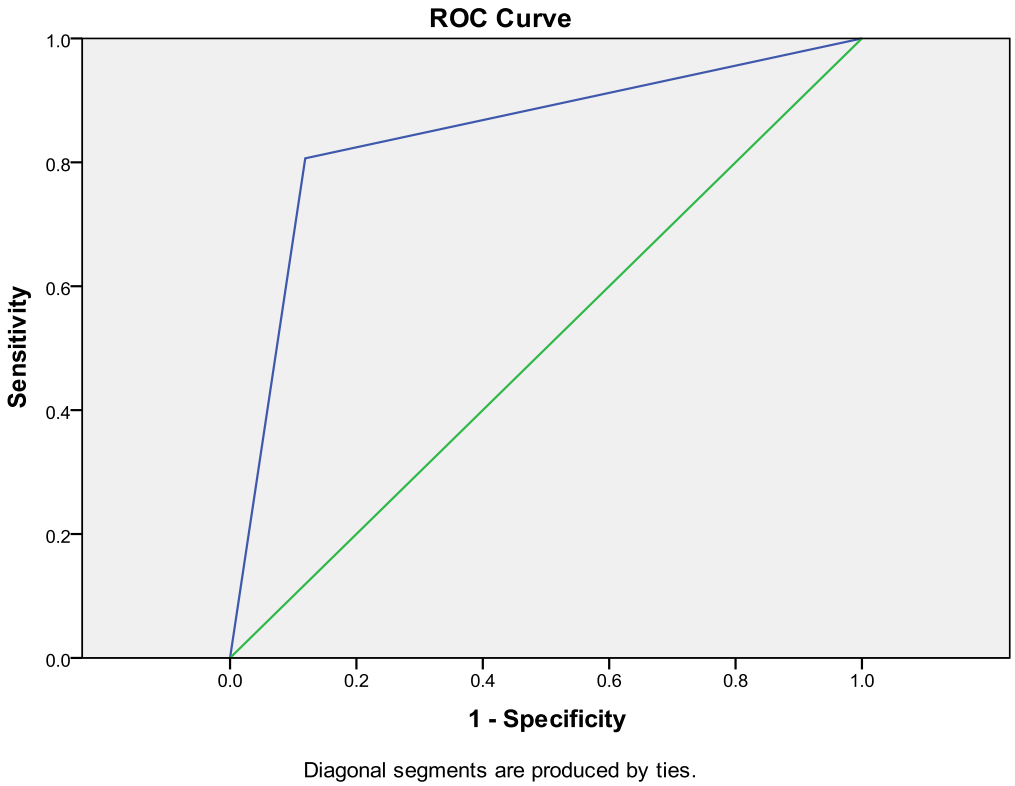
DATA	PCR >30	PCR <30	P value
TOTAL	29 (78.4%)	8 (21.6%)	
MALE	18 (62.1%)	3 (37.5%)	
FEMALE	11 (37.9%)	5 (62.5%)	
AGE, in median	16 months (2-130)	84 months (2-108)	
Length of Stay(days), mean	9.43 ± 5.21	6.89 ± 3.18	
MORTALITY	17 (58.6%)	3 (37.5%)	0.001
RRT	10 (34.5%)	1 (12.5%)	0.001

TABLE IV: PERFORMANCE OF PCR>30 IN PREDICTION OF DEVELOPMENT OF AKI

DATA	OUR STUDY
SENSITIVITY %(95% CI)	85.4 (66.2 – 95.3)
SPECIFICITY %(95% CI)	88 (74 – 95.7)
POSITIVE PREDICTIVE VALUE %(95% CI)	81.6 (66 – 89.9)

NEGATIVE PEDICTIVE VALUE %(95% CI)	87.1 (76.7 – 94.3)
AUC (95%CI)	0.84 (0.72 – 0.90)

FIGURE I: ROC CURVE



DISCUSSION

Acute Kidney Injury following sepsis is still one of the dreadful complication and thus requires special attention as its early diagnosis and timely management may have some distinctive features. Identification of sepsis induced AKI as early as possible is of paramount importance in reducing the burden of disease per se and from its complications. Few clinical studies on critically ill children with severe endothelial and renal involvement have shown microalbuminuria may be a beneficial marker[12-13]. The changes in the glomerular structure following any type of acute kidney injury may precipitate the albumin filtration which presents as microalbuminuria[14,15].

In this study, the incidence of Acute Kidney Injury among children diagnosed with sepsis was found to be 39.8%. This was comparable with a study done by Idham Jaya Ganda et al[16], who found out the incidence of sepsis induced AKI to be 40% in their study. This study showed no significant differences in sex between the groups with sepsis who developed AKI. Similar results were shown in studies by Bresolin et al[17]. In the present study, microalbuminuria was present in 78.4% children with AKI. Similar findings was observed by study done by Nismath et al[18] which showed the presence of microalbuminuria in 79.8% study population. The sensitivity, specificity, positive predictive value and negative predictive value obtained from our study were comparable with study done by Anil et al[19].

This study prospectively included a group of children with sepsis who at presentation were thought to have normal kidney function (as defined by serum creatinine levels) yet considered at high risk of developing AKI. This study also demonstrates that microalbuminuria is common in children with sepsis and that the quantification of microalbuminuria is important. A urine protein to creatinine ratio of >30 is both a sensitive and specific marker for predicting development of AKI and mortality.

CONCLUSION

Urine protein:creatinine ratio appears to be a simple, rapid, non invasive, sensitive, specific and an easily applicable marker of risk of development of AKI in sepsis children. A urine protein:creatinine ratio of >30 is a significant risk factor for AKI. The findings of this study indicated the need to investigate the role of urine protein:creatinine ratio in develoment of AKI in sepsis children. Kidney function in children differs depending on age. Investigation according to age in a large number of patients is needed. Urine protein:creatinine ratio may be considered to be included as a part of a routine screening tool, in children with sepsis, to risk stratify those patients who are at increased risk of AKI.

BIBLIOGRAPHY

1. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, Beginning, Ending Supportive Therapy for the Kidney I. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA; 294: 813-8; 2005.
2. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. Curr Opin Crit Care; 17: 153-9; 2011
3. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med. 2004; 351: 159-69.
4. Adler C, Reuter H, Seck c, Hellmich M, Zobel C, Fluid therapy and acute kidney injury in cardiogenic shock after cardiac arrest. Resuscitation. 2013; 84: 194-9.
5. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348(2):138–50. http://dx.doi.org/ 10.1056/NEJMra021333.
6. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003;101 (10):3765–77. http://dx.doi.org/10.1182/blood-2002-06-1887.
7. Gosling P. Microalbuminuria: a marker of systemic disease. Br J Hosp Med 1995;54(6):285–90.
8. De Gaudio AR, Adembri C, Grechi S, Novelli GP. Microalbuminuria as an early index of impairment of glomerular permeability in postoperative septic patients. Intensive Care Med 2000;26(9):1364–8. http://dx.doi.org/10.1007/s001340000593.
9. Szakmany T, Molnar Z. Increased glomerular permeability and pulmonary dysfunction following major surgery: correlation of microalbuminuria and PaO/FiO ratio. Acta Anaesthesiol Scand 2004;48(6):704–10. http://dx.doi.org/10.1111/j.1399-6576.2004..
10. Yew WS, Pal SK. Correlation of microalbuminuria and outcome in patients with extensive burns. Br J Anaesth 2006;97(4):499–502. http://dx.doi.org/10.1093/bja/ael211.
11. Mehta RL, Kellum JA, Shah SV et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.
12. MacKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E. Use of microalbuminuria as a predictor of outcome in critically ill patients. Br J Anaesth 2000;84(2):239–41.
13. Abid O, Sun Q, Sugimoto K, Mercan D, Vincent JL. Predictive value of microalbuminuria in medical ICU patients: results of a pilot study. Chest 2001;120(6):1984–8.
14. Solez K, Racusen LC, Whelton A: Glomerular epithelial cell changes in early postischemic acute renal failure in rabbits and man. Am J Pathol 103:163-173, 1981
15. Avasthi PS, Evan AP, Huser JW, et al: Effect of gentamicin on glomerular ultrastructure. J Lab Clin Med 98:444-454, 1981
16. Idham Jaya Ganda, Karjana, Dasril Daud. Association between sepsis induced acute kidney injury with shock and length of stay in critically ill paediatric patients. Curr Pediatr Res 2019; 23(2): 64-70.
17. Bresolin N, Bianchini AP, Haas CA. Paediatric acute kidney injury assessed by pRIFLE as a prognostic factor in the intensive care unit. Pediatr Nephrol 2013; 28: 485-492.
18. Shifa Nismath, Suchetha S. Rao, B.S. baliga, Vaman Kulkarni et al. Comparative validity of microalbuminuria versus clinical mortality scores to predict pediatric intensive care unit outcomes. Clinical and Experimental Pediatrics 2020;63(1): 20-24.
19. Anil AB,Anil M, Yildiz M, Kamit Can F, Bal A, Gokalp G et al. The importance of microalbuminuria in predicting patient outcome in PICU. Pediatr Crit care Med 2014; 15: e220-5.