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Assessment of Urine Albumin Creatinine Ratio in Renal Injury in Septic Children and Its Relation to Outcome

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ABSTRACT

Background: The paediatric intensive care unit (PICU) is critical in providing demanding and necessary treatment to very unwell children. PICU children have a much greater risk of morbidity and mortality in both underdeveloped and developed nations.

Objective: The aim of this study was to assess the urine albumin creatinine ratio (ACR) in renal injury in septic children and it's role in predicting outcome.

Patients and Methods: This study was carried out in Pediatric Intensive Care Unit and clinical pathology department at Zagazig University Hospitals in the period from April 2022 to October 2022. It was approved by Institutional Review Board- Zagazig University (IRB 9482). Written informed consent was taken from all parents.

Results: This study included 68 patients with median age 1 year, females represented 47.1% of them and males were (52.9%). Our study revealed that, blood culture was positive in 80.9% of patients and 44.1% had sepsis degree 3 .In the current study, median albumin/creatinine ratio on admission was 319 mg/g which significantly decreased to 253 mg/g after 24 hours. Our study showed that, there is statistically significant relation between mortality and ACR on admission and after 24 hours (significantly higher in those with non-survivors). In non-survivors, there was significant increase in ACR while there was significant decrease in ACR in survivors after 24 hours. Concerning trend for ACR, 97.1% of non-survivors had increasing ACR after 24 hours versus one patient of survivors.

Conclusion: Elevated urinary ACR is associated with the severity of sepsis, morbidity, and mortality.

Keywords: Urine Albumin Creatinine Ratio - Assessment – Renal Injury - Septic Children**.**

INTRODUCTION

Even in developed nations, sepsis remains one of the main causes of mortality in children. Many children who are said to die from various underlying diseases really pass away from sepsis, despite the fact that demographic data does not clearly demonstrate this [(1)].

It might be difficult and extremely important to predict morbidity and death in paediatric critical care units. Making the proper judgements and resulting improvements in outcomes are made possible through accurate prediction. To forecast PICU outcomes, a variety of clinical metrics are utilised, including the paediatric risk of mortality (PRISM) score, paediatric logistic organ dysfunction (PELOD) score, and paediatric index of mortality 2 (PIM 2). In developed country ICU settings, these scores have been verified. These scores must be calculated using a variety of characteristics and online resources [(2)].

Inflammatory reaction damages the endothelium membrane in critically sick patients, which is followed by an increase in capillary permeability and temporary albuminuria. Albuminuria can vary in severity, and the majority of cases are not detected by urine dipstick protein quantification, thus the term "microalbuminuria". Spot urine albumin creatinine ratio (ACR) tests can detect microalbuminuria [(3)]. The ACR is a straightforward, uncomplicated, and non-invasive measurement that can accurately predict PICU outcomes [(4)].

In children with sepsis, severe sepsis, septic shock, and MODS, it was expected that a greater urine albumin:creatinine ratio (ACR) would increase disease severity and organ dysfunction, as well as be a predictor of death and morbidity [(5)].

The aim of this study was to assess the urine albumin creatinine ratio in renal injury in septic children and it's role in predicting outcome.

PATIENTS AND METHODS

This study was carried out in Pediatric Intensive Care Unit and clinical pathology department at Zagazig University Hospitals in the period fromApril 2022 to October 2022.

A) Patients:

From 200 patients admitted to Pediatric Intensive Care Unit, Children's Hospital Zagazig University. Sixty eight patients were included aged between 1month and 14 years, critically ill patients, diagnosed as sepsis by Systemic inflammatory response syndrome (SIRS) criteria and documented infection. SIRS is an exaggerated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy, to name a few) to localize and then eliminate the endogenous or exogenous source of the insult [(6)].

Pediatric SIRS criteria[(7)] :

The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**

-. Core temperature o f >38.5°C or <36°C.

-.Leukocyte count elevated or depressed for age or >

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10% immature neutrophils.
- Tachycardia defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus,or **for children <1 yr old: bradycardia, defined as a mean heart rate <**10th percentile for age in the absence of external vagal stimulus.
-Mean respiratory rate >2 SD above normal for age or need for mechanical ventilation

Sepsis was classified into 3stages:
-**Sepsis:** SIRS+ infection (or suspected infection).
-**Severe sepsis:** Sepsis + CV dysfunction or ARDS or 2 other dysfunctional organs.
-**Septic shock:** Sepsis+ CV dysfunction.

Exclusion criteria:

- Patients with chronic renal disease.
- Acute kidney injury.
- Urinary tract infections.
- Nephrotic syndrome.
- Acute glomerulonephritis.
- Nephrotoxic drugs.

B) Methods:
Operational design:
All participants were subjected to the followings:
1-Subjective global assessment (full history taking: name, age, sex).
2- Routine laboratory testing including:
(a) Complete Blood Count: done on automated cell counter, model XN 330 (Sysmex, Japan). (b) Coagulation profile: done on automated blood coagulation analyzer,model CS 2100 (Sysmex, Japan). (c) Blood chemistrytesting including Liver and kidney function tests, Blood glucose. Procalcitonin and C-reactive protein. These tests performed on Roche Cobas 8000 auto analyzer, using dedicated reagents supplied by the manufacturer (Roche diagnostics, Switzerland). (d) Arterial blood gases and electrolytes by Blood Gas Analyzer (ABL800 Flex, Radiometer, Denmark).
3- Bacteriological examination: Blood culture, Cultures were done to samples from different sites included: tracheal aspirate, CSF, urine and CVC according to every case.
4- Specific research test: (Measurement of albumin creatinine ratio).

The test was performed on admission within 1 h and after 24 hrs. It was performed on Cobas 6000 auto analyzer, series c501, using dedicatedreagent according to manufacturer recommendation (Roche diagnostics, Switzerland).

Test principle: immunoturbidemetric assay for urine albumin while kinetic colorimetric assay which is based on Jaffe method was used for urine creatinine estimation.

Ethical approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, El- Zagazig University (IRB 9482). All participants parents provided written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

Statistical software for social science (SPSS) was used to code, input, and analyse the data (version24). The outcomes were tabulated and diagrammed, and then they were interpreted. As descriptive statistics, mean, standard deviation, range, frequency, and percentage were used. For categorical data, the association factors were examined using the Chi-Square test X^2. In a research using independent samples, the statistical significance of the difference between two population means was evaluated using the Student's t-test. ANOVA (F test) for typically quantitative variables, Post Hoc test (LSD) for pairwise comparisons, and ANOVA (F test) for comparisons between more than two groups. P value less than 0.05 was regarded as significant.

RESULTS

This study included 68 patients with age range from one month to 14 years and females represented 47.1%. Larger percentage of patients (91.2%) had round regular reactive pupil. Forty patients (58.8%) underwent mechanical ventilation and forty three patients received inotropes and 44.1% had sepsis degree 3. Regarding outcome, thirty three patients survived till discharge (48.5%). Length of PICU stay ranged from 5 to 28 days with median 15.5 days **(Table 1).**

Table (1): Distribution of studied patients according to their characteristics:

		N=68	%
Gender:	Female	32	47.1%
	Male	36	52.9%
		Median (IQR)	**Range**
	Age (months):	1 (6 months – 6 years and 9 months)	One month – 14 years
MV:	No	28	41.2%
	Yes	40	58.8%
Inotropes	Yes	43	63.2%
	No	25	36.8%
	Pupillary reaction		
	Irreactive	1	1.5%
	Dilated fixed	1	1.5%
	RRR	62	91.2%
	Unequal	4	5.9%
	GCS	9.4 ± 2.35	4 – 14
	Sepsis degree		
	sepsis	22	32.4%
	sever sepsis	16	23.5%
	septic shock	30	44.1%
	Length of PICU stay	15.5 (8 – 19)	5 – 28
	Outcome		
	Survivors	33	48.5%
	Non-survivors	35	51.5%

MV: mechanical ventilation, **GCS**: Glassco Coma Scale, **RRR:** round, regular, reactive

Mean hemoglobin was 9.85 g/dl. Median white blood cells was 11.9 (10^3/mm^3) and that for platelet was 80 (10^3/mm^3). Median procalcitonin was 6.3 median bilirubin, creatinine, and blood glucose were 1.9, 0.2 and 74.5 mg/dl. Mean serum potassium, and calcium were 3.54, and 8.57 mg/dl respectively. Mean PaO2/FiO2 was 201.34 and mean PaCO2 was 63.24. Blood culture was positive in 80.9% of patients **(Table 2)**.

Table (2): Laboratory data of studied patients:

	Mean ± SD	
Hemoglobin (g/dl)	9.85 ± 1.94	
Serum potassium (mEq/L)	3.54 ± 0.99	
Serum calcium (mg/dl)	8.57 ± 1.11	
Serum bicarbonate (mEq/L)	20.57 ± 5.11	
PaO_2/FiO_2	201.34 ± 48.34	
$PaCO_2$ (mmHg)	63.24 ± 13.91	
	Median (IQR)	**Range**
WBCs (10^3/mm^3)	11.9 (8.13 – 19.98)	0.1 – 33
Platelet count (10^3/mm^3)	80 (29 – 134)	10 – 573
CRP	63 (38.73 – 98.75)	10 – 453
Procalcitonin	6.3 (3.63 – 18.25)	0.8 – 100
Total bilirubin (mg/dl)	1.9 (1.03 – 2.88)	0.1 – 8
PT	14 (12.4 – 16)	11 – 41
PTT	36 (33.4 – 49.75)	19.5 – 77
Creatinine (mg/dl)	0.2 (1 – 0.3)	0.04 – 0.9
Blood glucose (mg/dl)	74.5 (54.5 – 91)	19 – 230
	N=68	**%**
Blood culture		
Negative	13	19.1%
Positive	55	80.9%

Median (IQR), range: non-parametric test.

Median albumin/creatinine ratio on admission was 319 mg/g which significantly decreased to 253 mg/g after 24 hours. Thirty-five patients (51.5%) had increasing ACR and 33 patients had decreasing ACR **(Table 3)**.

Table (3): Distribution of studied patients according to ACR on admission and after 24 hours:

	Median (IQR)	Range	P
On admission	319 (119.75 – 766.25)	32 – 9212	<0.001**
After 24 hours	253 (94.25 – 897.5)	6.6 – 5340	
% change in ACR	35.1 (-59.33, 132.75)		
	N=68	**%**	
Increasing ACR	35	51.5%	
Decreasing ACR	33	48.5%	

p for Wilcoxon signed rank test **p≤0.001 is statistically highly significant

There is statistically significant relation between mortality and ACR on admission and after 24 hours (significantly higher in those with non-survivors). In non-survivors, there is significant increase in ACR while there is significant decrease in ACR in survivors after 24 hours. Concerning trend for p-SOFA, 97.1% of non-survivors had increasing ACR after 24 hours versus one patient of survivors **(Table 4)**.

Table (4): Relation between outcome and ACR on admission and after 24 hours:

Parameter		Outcome		Test	
		Non-survivors	Survivors	χ^2	p
		N=35 (51%)	N=33(48.5%)		
Change in ACR	Increasing Decreasing	34 (97.1%) 1 (2.9%)	1 (3%) 32 (97%)	Fisher	<0.001**
ACR on admission	Median IQR	703 255 – 1030	149.6 92.05 – 350.5	-3.755	<0.001**
ACR after 24 hours	Median IQR	852 323 – 2134	94 52.05 – 144.5	-6.301	<0.001**
	P (Wx)	<0.001**	<0.001**		

Z Mann Whitney test IQR interquartile range χ^2 Chi square for trend test **p≤0.001 is statistically highly significant Wx Wilcoxon signed rank test

Table (5): Relation between outcome and laboratory data

	Outcome		Test	
	Non-survivors (n=35)	Survivors (n=33)	t	p
	Mean ± SD	Mean ± SD		
Hemoglobin (g/dl)	9.41 ± 2.02	10.32 ± 1.76	-1.985	0.051
PT	17.01 ± 3.71	13.72 ± 3.23	2.685	0.01*
PTT	46.16 ±10.31	35.96 ±8.54	3.253	0.002*
S potassium(mg/dl)	3.31 ± 0.84	3.79 ± 0.77	-2.048	0.045*
Serum calcium (mg/dl)	8.14 ± 1.05	9.02 ± 1.0	-3.543	0.001**
Serum bicarbonate (mEq/L)	20.6 ± 4.78	20.55 ± 5.01	0.031	0.975
PaO_2/FiO_2	179.86 ± 42.98	224.12 ± 53.54	-2.489	0.006*
$PaCO_2$ (mmHg)	63.91 ± 11.4	56.79 ± 3.56	-4.132	<0.001**
	Median(IQR)	**Median(IQR)**	**Z**	**p**
Blood glucose (mg/dl)	67 (44 – 90)	80 (69 – 92)	-1.837	0.066
WBCs ($10^3/mm^3$)	13 (8.5 – 20)	11 (7.2 – 19.45)	-0.786	0.432
Platelet count($10^3/mm^3$)	40 (19 – 102.5)	112 (38 – 144)	-2.792	0.005*
Creatinine (mg/dl)	0.2(0.2 – 0.3)	0.2(0.1 – 0.3)	-1.575	0.115
Total bilirubin (mg/dl)	2.8 (1.85 – 3.75)	1.3 (0.7 – 1.9)	-4.021	<0.001**
Procalcitonin	8 (5 – 32)	6 (3 – 9.75)	-2.614	0.009*
CRP	86 (50 – 156)	50 (28 – 78)	-2.995	0.003*
	N=35 (%)	N=33(%)	χ^2	p
Blood culture Negative Positive	12 (34.3%) 23 (65.7%)	1 (3.0%) 32 (97.0%)	10.731	<0.001**
Sepsis grade: Sepsis Sever sepsis Septic shock	1 (2.9%) 5 (14.3%) 29 (82.9%)	21 (63.6%)[¥] 11 (33.3%) 1 (3%)[¥]	53.386[§]	<0.001**

Median (IQR): non parametric test.

Z: Mann Whitney test. t: independent sample t test. [¥]: significantly differ between groups. χ^2: Chi square test. [§]: Chi square for trend test. [¥]: significantly differ between groups. **p≤0.001 is statistically highly significant.

There was statistically **significant** elation between mortality and PT, PTT, serum potassium, serum calcium, PaO2/FiO2, PaCO2, platelet count, total bilirubin, procalcitonin and CRP. There was statistically non-**significant** elation between mortality and hemoglobin, white blood cells, creatinine, or serum bicarbonate.

There was statistically **significant** relation between mortality and blood culture. Negative blood culture **significantly** associated with mortality.

There was statistically **significant** relation between mortality and sepsis degree. Sepsis degree 1 **significantly** prevailed in survivors and degree 3 **significantly** prevailed in non-survivors.

DISCUSSION

This was a cohort study that was carried out in Pediatric Intensive Care Unit, Children's Hospital Zagazig University on 68 cases with median age 1 year, females represented 47.1% of them and males were (52.9%), admitted to PICU aged between 1 month and 14 years diagnosed as sepsis and documented infection.

Our research supports that of **Tariq *et al.* [8],** who assessed Microalbuminuria (MAU) as a predictor of patient outcome in a paediatric critical care unit of 250 patients, 145 of whom were male (58%) and 105 of whom were female (42%).

In the current study, median albumin/creatinine ratio on admission was 319 mg/g which significantly decreased to 253 mg/g after 24 hours. Thirty-five patients (51.5%) had increasing ACR and 33 patients had decreasing ACR.

This was in agreement with research by **Sachdev *et al.* [5]** that the ACR exhibited growing trends as sepsis severity increased. The pathogenetic events of gradual microcirculatory damage with increasing sepsis severity corroborate this observation.

Many population-based studies define MAU as an excretion rate of 30-300 mg/24 hours of urinary albumin in a 24-hour urine sample [9].

Urinary albumin/creatinine ratios may serve as indicators of endothelial dysfunction brought on by systemic inflammation, and they will typically decline when inflammation is reduced [10].

According to **Saragih *et al.* [11]** who sought to examine the relationship between serum syndecan-1 levels and urine ACR levels. They examined the urine ACR in healthy children aged 1-35 months and discovered that the median value was 10.5 (3-88) mg/g. In healthy people, the urine ACR was shown to be less than 30 mg/g. Comparing the septic group to the healthy group, it was discovered that urinary ACR was higher in the septic group. On day 1, 11 participants had urine ACRs between 30 and 300 mg/g, making up a total of 33 subjects (67.3%) with urinary ACRs over 300 mg/g.

According to research by **Basu *et al.* [12]** 78% of patients admitted to the ICU had microalbuminuria, with a median value of 125.6 mg/g. After 24 hours, 67% of patients still had microalbuminuria, but the median value had dropped to 62.6 mg/g.

In our study regarding outcome, thirty-three patients survived till end of study (48.5%). A mortality rate 33.1% was reported from Abo El-Reesh hospital in Egypt by **Rady *et al.* [13]**, and in Saudi Arabia was (37.4%) as reported by **Alsuheel *et al.* [14].**

Our study showed that, there is statistically significant relation between mortality and ACR on admission and after 24 hours (higher in non-survivors and lower in survivors)''. In non-survivors, there was significant increase in ACR compared to ACR in survivors on admission and after 24 hours ($p<0.001$).

Concerning trend for ACR, 97.1% of non-survivors had increasing ACR after 24 hours versus one patient of survivors.

Similar to this, according to **Sachdev *et al.* [5],** serial levels of ACR were persistently higher in nonsurvivors, and in the first 24 hours following admission, ACR in survivors significantly decreased. They found a substantial correlation between morbidity and death and an ACR level >102 mg/g at the time of admission, 12 hours after admission, and 24 hours after admission

In a 2010 study, individuals who died of sepsis had increased levels of microalbuminuria within the first 24 hours [11].

Sachdev *et al.* [5] found that ACR > 102 mg/g was significantly linked with mortality, a need for inotropes, and a longer period of mechanical breathing, and that ACR and pediatric logistic organ dysfunction (PELOD) and pediatric risk of mortality (PRISM) scores had a strong association.

In our study there was statistically significant positive correlation between albumin/creatinine ratio on admission, after 24 hours and sepsis degree.

A study conducted by **Basu *et al.* [12]** the degree of microalbuminuria within 6 hours of admission was significantly higher in patients with sepsis at a median ACR of 206.5 mg/g.

In our study, there was statistically significant relation between mortality and sepsis degree. Sepsis degree 1 significantly prevailed in survivors and degree 3 significantly prevailed in non-survivors

The stage at which sepsis is identified also affects the likelihood of survival, since those who are initially clinically identified as having septic shock have a higher risk of passing away within 28 days. Further raising mortality risks within the first week is the development of severe sepsis and/or septic shock [15].

In our study regarding outcome, thirty-three patients survived till end of study (48.5%).

The mortality rate was 33.1% reported from Abo El-Reesh hospital in Egypt by **Rady *et al.* [13]**, Saudi Arabia (37.4%) by **Alsuheel *et al.* [14]** and India (24.3%) by **Taori *et al.* [16]**.

Our mortality rates were similar to Indonesian study performed by **Sari *et al.* [17]** where the mortality

was (40.58%), **Honna *et al.* [18]** (45.7%) and the Indian study by **Gandi *et al.* [19]** (46.2%).

CONCLUSION

Elevated urinary ACR is associated with the severity of sepsis, morbidity, and mortality.

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Competing interests: Nil.

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