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Association between sepsis induced acute kidney injury with shock and length of stay in critically ill pediatric patients.

Idham Jaya Ganda*, Karjana, Dasril Daud

Faculty of Medicine, Department of Pediatrics, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Abstract

Introduction: Sepsis induced AKI is reversible increase in serum creatinine levels or nitrogen metabolism products and the inability of the kidneys to regulate fluid and electrolytes to a state of body homeostasis caused by sepsis. This study aimed to find out relationship between sepsis-induced AKI and shock and length of stay in Pediatric Intensive Care Unit (PICU).

Methods: This prospective cohort study was conducted in PICU from November 2017 to October 2018. A total of 90 sepsis patients were included. The diagnostic of septic shock based on International Pediatric Sepsis Consensus 2015. Kidney function examination and urine production every 8 hours was done to determine whether or not Acute Kidney Injury present. Patient were observed until the outcome occurred; either septic patient become shock or not and how long they were treated in PICU.

Results: Result of 90 sepsis patients, 36 patients (40%) become sepsis-induced AKI. Chi Square analysis found significant differences in the incidence of shock in sepsis-induced AKI patient with p=0.00 with OR 4.37, 95% CI 1,689 - 11.33. Sepsis patient with AKI will undergo longer treatment in PICU if compared to sepsis patients without AKI. However, Mann-Whitney test showed not significant (p=0.25).

Conclusion: Incidence of sepsis-induced AKI in this cohort of children was 40%, and shock severity in patients with sepsis induced-AKI was higher than those with sepsis without AKI, and there was no difference in length of stay between sepsis patients with AKI and without AKI.

Keywords: Sepsis, Septic shock, Acute kidney injury, Length of stay

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Introduction

Sepsis and septic shock is one of the causes of morbidity and mortality (50-60%) of children treated in inpatient and intensive care rooms. The mortality rate is higher in immunodeficient children [1-3]. The incidence of sepsis was higher in the neonate group and < 1 year old infants compared with age >1-18 years (9.7 versus 0.23 cases per 1000 children). Severe sepsis patients are mostly caused by respiratory tract infections (36-42%), bacteremia, and urinary tract infections. In the intensive care unit of the Cipto Mangunkusumo Hospital (RSCM), a total of 19.3% of 502 pediatric patients treated had sepsis with a mortality rate of 54% [4,5]. Severe sepsis is more common in children with comorbidities which results in a decrease in the immune system such as malignancy, transplantation, chronic respiratory disease and congenital heart defects [1,2,6]. The incidence of septic shock and severe sepsis has increased in the last 30-40 years. The incidence of severe sepsis in the United States is 0.56 cases per 1000 population per year. The highest incidence is in the infant age group (5.16 cases per 1000 population per year) and decreases sharply in the age group 10-14 years (0.2 cases per 1000 population per year). More than 4300 deaths per year or around 7% of total deaths in children are caused by severe sepsis [6].

Acute kidney injury (AKI) is defined as an increase in serum creatinine levels or nitrogen metabolism products which is sudden and reversible and the inability of the kidneys to regulate fluid and electrolytes to a state of body homeostasis and can be accompanied by or not reduced diuresis [7].

Children with critical illness have a greater chance to experience AKI. Around 5-12% of children treated in ICU experience AKI with various degrees.8 Most recently, a meta-analysis involving 154 studies of more than 3,000,000 people revealed that one in five adults and one in three children worldwide experienced AKI during one period of hospital care [10]. Some researchers found that the incidence of AKI in pediatric patients with critical illness ranged from 4.4% - 54.5% with sepsis as the main cause [8,10-12].

Acute kidney injury is a significant factor affects the morbidity

and mortality of pediatric patients and neonates admitted to intensive care. The number of patients with AKI treated in PICU ranged from 48% - 68%. AKI occurs in 19% of patients with severe sepsis, 23% in patients with moderate sepsis and 51% in patients with septic shock. The combination of the incidence of AKI with sepsis has a mortality rate of 70%, compared with a mortality rate of 45% in patients with sepsis alone [13]. James et al. [14] in a retrospective analysis study found that patients treated with AKI had twice the length of stay compared to those without AKI and those who had AKI while in PICU would receive treatment 4 times longer.

In sepsis, there will be changes and disturbances in glomerular filtration pressure and in the intra-renal distribution of blood flow, inflammation, oxidative stress, apoptosis, microcirculation disorders, mitochondrial dysfunction, and inter-organ communication that can cause AKI. Sepsis patients with AKI also showed an increase in levels of High Mobility Group Box 1 (HMBG1). HMBG1 released into extracellular fluid acts as Damage Associated Molecular Pattern (DAMP) which mediates the inflammatory response that stimulate production of pro-inflamation cytokine (TNF-α) [15]. It can affect endotelial dysfunction (vasodialtation and plasma leakage) and myocard dysfunction which can lead to shock. Besides that, AKI can cause oligouri, imbalance electrolytes, acidemia, uremia, fluid overload, and activation of renin angiotensin aldosteron system that can cause myocard dysfunction which lead to shock [16].

Materials and Methods

This study was an observational study with a prospective cohort method. The study variables consist of independent variable (sepsis and AKI), dependent variable (outcome (shock, not shock, length of stay in PICU), intermediate variable (sepsis and biological process of shock), random variable (age, sex and genetic) and control variable (malnutrition, corticosteroid, trauma, burn injury, malignancy, and AKI).

This study was conducted in the Pediatric Intensive Care Unit of DR Wahidin Sudirohusodo General Hospital Makassar during November 2017 until October 2018. C - reactive protein, leukocyte, ureum and creatinin was analysed at laboratory of Dr. Wahidin Sudirohusodo General Hospital.

The study population was all patients aged 1 month - 18 years who were diagnosed with sepsis who were admitted to the Pediatric Intensive Care Unit (PICU) of Dr. Wahidin Sudirohusodo General Hospital Makassar. The study sample was the entire possible population that met the inclusion and exclusion criteria. The method of taking samples is consecutive sampling, which is the subject of research obtained based on the order of entry in the hospital.

Inclusion criteria in this study were patients with sepsis, age 1 month to 18 years who underwent hospitalization at PICU. Exclusion criteria were patients with trauma, burns injury, malnutrition (severely wasted type of malnutrition), currently getting corticosteroids, immunodeficiency, malignancy, shocked, previous kidney problems, and currently having acute kidney injury.

In this study, every action is carried out after obtaining permission from ethics commision DR Wahidin Sudirohusodo General Hospital and Biomedical Research in humans Faculty of Medicine Hasanuddin University Makassar and informed consent from parents of babies/ patients to be used as research samples.

Children aged 1 month - 18 years were diagnosed with sepsis based on International Pediatric Sepsis Consensus 2015. The stage of acute kidney injury is according to pRIFLE staging by calculating eGFR according to Schwartz's formula and the amount of urine production. Shock manifests as fast and weak pulse, poor tissue perfusion (CRT>3 seconds), urine output <0.5 ml/ kg/ hour, narrowing of pulse pressure (≤ 20 mmHg) or hypotension. Duration of Stay is the period of time the child is hospitalized in PICU since being diagnosed with sepsis and GnGA due to sepsis, expressed in days. Vital signs (temperature, pulse, blood pressure, breathing frequency), consciousness, clinical symptoms, and diagnosis were recorded. Kidney function examination and urine production every 8 hours was done to determine whether or not Acute Kidney Injury present. During the treatment in the PICU, the study subjects were observed until the outcome occurred; either septic patient become shock or not and how long to be treated in PICU. All the obtained data were recorded in the research data form and then grouped by destination and type and analysed by using univariate and bivariate analysis (Significant if $p<0.05$).

Univariate analysis was used to describe basic data in form of frequency distribution, average value, standard deviation and range. In bivariate analysis, Chi square test, Kolmogorov-Smirnov, Mann-Whitney, and Kruskal-Wallis was chosen. Chi Square test was used to is to determine the significance relationship between prognostic factors and outcomes in form of shock and non-shock in patients experiencing acute renal impairment due to sepsis.

Results

During the study period, there were 171 sepsis patient treated in PICU Wahidin Sudirohusodo General Hospital. Out of the total sample, 81 patients were excluded with details; 10 malnutrition cases (severely wasted), 15 malignancy cases (leukemia, retinoblastoma, neuroblastoma and nephroblastoma); 33 surgical and trauma cases, 5 cases with previous kidney disease (nephrotic syndrome and lupus nephritis), 2 cases of patients who had experienced hypovolemic shock before AKI, 2 cases diagnosed with sepsis and AKI at PICU care, 6 cases with congenital abnormalities (Pierre Robin Syndrome, and congenital heart disease), and 8 cases with a combination of the above disorders. So there were 90 samples of children with sepsis who met the inclusion criteria. All samples that met the inclusion criteria were observed whether they had AKI or not and observed whether they were shocked or not shocked and then counted the number of days of treatment in the PICU. From 90 samples, 36 (40%) children had AKI and 54 (60%) did not experience AKI. Out of 36 patients with AKI (Sepsis-Induced AKI), 28 (77.8%) children were shocked and 8 (22.2%) children were not shocked, while of sepsis patient who did not have AKI, 24 (44.4%) patient had no shock and 30 (55.6%) patient had shocked. Then statistically analyzed to assess the relationship between each variable.

Sepsis is an organ dysfunction caused by immune system dysregulation to infection. Therefore, in diagnosing sepsis, it is very important to know the focus of infection. Most focus infection in this study was Community Acquired Pneumonia 49 patient (54.5%), tuberculous meningitis 9 patient (10%), encephalitis 8 patient (8.9%), urinary tract infections 5 patient (5.6%), meningitis 4 patient (4.4%), typhoid fever 3 patient (3.3%) and pulmonary tuberculosis 2 patient (2.2%). In addition there are also cases of sepsis with more than one focus of infection, which is found in 10 patients (11.1%) in the form of community acquired pneumonia and urinary tract infections, Community acquired pneumonia and meningitis, and community acquired pneumonia and skin infections (piodermi).

Table 1 shows that out of a total of 90 samples of children with sepsis, there were 37 boys (41.11%) and 53 girls (58.89%). A total of 15 boys (40.6%) had AKI and 22 (59.5%) did not experience AKI. While for girls, 21 children (39.6%) had AKI and 32 children (60.4%) did not experience AKI. Chi Square analysis reveal there is no significant difference in the incidence of AKI between boys and girls (p=0.93) Based on the incidence of shock, 24 boys (64.9%) suffered shock and 13 (35.10%) did not experience shock. Whereas girls, 28 children (39.6%) suffered shock and 25 children (47.2%) did not experience shock. Chi-square test reveal incidence of shock was not significantly different between girls and boys (p=0.25).

It was found that 24 children (26.67%) were undernourished and 66 children (73.33%) had normal nutritional status. Children who were undernourished, 12 children (50%) have AKI and 12 children (50%) did not. In children with normal nutrition state, 24 children (36.4%) had AKI and 42 children (63.6%) did not. Chi square test produced p=0.24, so there was no significant difference in the incidence of AKI between children with sepsis and normal nutrition and those with undernourished. While based on the incidence of shock, 16 sepsis patients with malnutrition (66.7%) experienced shock and 8 patients (33.3%) did not. In children with sepsis with normal nutrition, 36 children (54.5%) experienced shock and 30 children (45.4%) did not experience shock. Chi square test showed there was no significant difference in the incidence of shock between septic patients with normal nutrition and those with sepsis accompanied by malnutrition (p=0.30).

Age characteristics, body temperature, blood leukocyte count, and CRP levels in the sample can be seen in Table 1. After the normality test using the Kolmogorov-Smirnov test, it was found that sample characteristics for age, temperature, leukocyte count, and CRP levels at PICU entry were not normally distributed (p values respectively sequentially p=0.00, p=0.03, p=0.00, and p=0.00) so Mann-Whitney test was used to compare each characteristic.

The statistical analysis in Table 2 shows that children with AKI has an average age of 1.74 years, a median value of 0.58 years and a range of 0.17-15.42 years, while those without AKI have an average age of 3.39 years, median 1.33 years

Table 1. *Sample characteristic based on their sex and nutritional status, age, temperature, leukocyte count, CRP level with AKI incidence and shock in sepsis, p=Chi Square; AKI: Acute Kidney Injury, *p=Mann-Whitney; AKI: Acute Kidney Injury; CRP=C reactive Protein.*

Variables	AKI		Total	p	Shock		Total	p
	Yes n (%)	No n (%)			Ya n (%)	No n (%)		
Sex								
Male	15 (40.6)	22 (59.5)	37	0.93	24 (64.9)	13 (35.1)	37	0.25
Female	21 (39.6)	32 (60.4)	53		28 (52.8)	25 (47.2)	53	
Nutritional state								
Malnutrition	12 (50)	12 (50)	24	0.24	16 (66.7)	8 (33.3)	24	0.3
Normal	24 (36.4)	42 (63.6)	66		36 (54.5)	30 (45.5)	66	
Age (years)								
Mean (SD)	1.74 (3.76)	3.39 (5.47)		0.13*	2.86 (4.45)	3.90 (5.68)		0.09*
Median	0.58	1.33			0.67	1.17		
(min-max)	(0.17-15.42)	(0.17-17)			(0.17-17)	(0.17-17)		
Temperature (°C)								
Mean (SD)	37 (1.17)	38.1 (1.21)		0.38*	38.1 (1.00)	37.89 (1.42)		0.41*
Median	37.9	38.4			38.25	37.6		
(min-max)	(36.1-40.3)	(36.1-40.4)			(36.10-39.9)	(36.1-40.4)		
Leukocyte Count ($\times 10^3/mm^3$)								
Mean (SD)	14.27 (7.21)	17.31 (10.43)		0.20*	15.23 (10.05)	17.23 (8.31)		0.16*
Median	15.6	16.2			15.85	16.2		
(min-max)	(4.2-30.1)	(2.6-49.5)			(2.6-49.5)	(6.8-43.2)		
CRP Level (mg/dl)								
Mean (SD)	50.9 (60.92)	53.82 (58.52)		0.87*	49.2 (65.37)	57.35 (49.91)		0.11*
Median	39.4	28.5			28	46		
(Min-Max)	(0.1-265)	(1-199.6)			(0.1-265)	(1.2-160.9)		

Table 2. *Association of AKI incidence with shock in septic children, p=Chi Square.*

Sepsis	Shock		Total	p	OR (95% CI)
	Yes n (%)	No n (%)			
Acute Kidney Injury					
Yes	28 (77.8)	8 (22.2)	36	0	4.37 (1.68 – 11.33)
No	24 (44.4)	30 (55.6)	54		

with a range of 0.17-17.00 years. Mann-Whitney test showed there was no significant difference in age between children who experienced AKI and those without with p=0.13. Based on the incidence of shock, it was found that children who had shock had an average age of 2.86 years, median age of 0.67 years with a range of 0.17-17.00 years and those who did not, have an average age of 3.9 years, median age of 1.17 year with a range of 0.17-17 years. The Mann-Whitney test showed results not statistically significant with p=0.09.

Child's body temperature at the time of entering the PICU who had AKI had an average of 37ºC, a median value of 37.9ºC and a range of 36.1-40.3ºC, while those without AKI had a mean value of 38.1ºC, median temperature 38,4oC with a range of 36.1-40.4ºC. Mann-Whitney test showed no significant difference in body temperature between children who had AKI and those without AKI with p=0.38. Based on the incidence of shock, children who had shock had a mean temperature of 38.1ºC, a median of 38.25ºC with a range of 36.10-39.9ºC and those without shock had a mean temperature of 37.89ºC, median 37.6ºC with a range of 36.1-40.4ºC. The Mann-Whitney test showed results not statistically significant with p=0.41.

Number of leukocytes of children with AKI have an average of 14.27 × 10^3/mm^3, a median value of 15.60 × 10^3/mm^3 and a range of 4.20-30.10 × 10^3/mm^3, while those who do not have AKI have a mean value of 17.31 × 10^3/ mm^3, median leukocytes 16.20 × 10^3/ mm^3 and range 2.60-40, 50 × 10^3/ mm^3. The Mann-whitney test produced a p value=0.20 which means there was no significant difference in the number of blood leukocytes of children with sepsis accompanied by AKI with no AKI. Based on the incidence of shock it was found that the number of leukocytes of children who had shock had an average value of 15.23 × 10^3/mm^3, a median of 15.85 × 10^3/mm^3 and a range of 2.60-49.50 × 10^3/mm^3, while those who did not experience shock had a mean value of 17.23 × 10^3/mm^3, median leukocytes 16.20 × 10^3/mm^3 and range 6.80-43, 20 × 10^3/mm^3. The Mann-Whitney test showed that there were no significant differences in the number of leukocytes between shocked septic patients and those without shock with p=0.16.

The CRP level of children with AKI has a mean value of 50.9 mg/dl, a median of 38.5 mg/dl and a range of 1.00-199.60 mg/dl, whereas those who do not have AKI have a mean value of 53.82 mg/dl, median CRP level 39.4 mg/dl and range 0.10-265 mg/dl. In the statistical test (Mann-Whitney) p value=0.87 which means that there is no significant difference between patients with sepsis with AKI and without AKI. Based on the incidence of shock, it was found that CRP levels in shocked children had an average value of 49.2 mg/dl, a median of 28.00 mg/dl and a range of 0.10-265.00 mg/dl, whereas those without shock had a mean value of 57, 35 mg/dl, median CRP level of 46.00 mg/dl and range of 1.20-160.90 mg/dl. There were no significant differences in CRP levels between septic patients who experienced shock and not shock with a value of p=0.11.

Table 3 shows CRP levels in sepsis patients who have AKI. In shocked patient, CRP levels have a mean of 47.30 mg/dl, median 37.20 with a range of 0.10-265.20 mg/dl while those who do not experience shock have a mean of 63.57 mg/dl, median 67.25 with a range of 8.00-140.00 mg/dl. There were no significant differences in CRP levels between septic patients who had AKI with shock and septic patients who had AKI without shock with a value of p=0.09.

Meanwhile, CRP levels in septic patients who do not have AKI but had shocked, CRP levels have a mean of 51.47 mg/dl, median of 18.50 with a range of 1.00-199.60 mg/dl while those without shock have a mean of 55.70 mg/dl, median 44, 50 with a range of 1.20-160.90 mg/dl. There were no significant differences in CRP levels between septic patients who did not have AKI but experienced shock with septic patients who did not have AKI and did not shock with a value of p=0.36.

Table 2 shows that in children with sepsis who have AKI, there are 28 children (77.8%) who are shocked and 8 (22.2%) children do not experience shock, while children without AKI 24 children (44.4%) experience shock and 30 children (55.6%) do not experience shock. Chi Square analysis found that there were significant differences in the incidence of shock between children who had AKI and did not experience AKI with a value of p=0.00 with OR 4.37, 95% CI 1,689-11.33. This can provide information that children who have sepsis accompanied by AKI have a 4.37 times chance of shock compared to children who have sepsis but are not accompanied by AKI.

In relation to the length of treatment in PICU, it can be seen from Table 4 that septic patients with AKI had a mean length of treatment of 10.05 days, median treatment for 10.5 days with a range of 1 to 21 days, while septic patients who did not have AKI had the mean length of treatment was 8.61 days, median length of stay was 7.5 days with a range of 3-19 days. Seeing this result indicates that sepsis patient with AKI will undergo treatment in PICU for longer if compared to septic patients without AKI. However, using the Mann-Whitney statistical test the results were not statistically significantly different between the length of treatment in PICU between patients with sepsis and AKI with no AKI with p=0.25.

Table 5 shows that of all children who have AKI, there were 10 children (27.78%) with AKI Risk, 8 children (22.22%) have AKI Injury stage and 18 children (50%) have AKI

Table 3. *Comparison of CRP levels between shock and non-shock in septic patients with and without acute kidney injury, P=Mann-Whitney; CRP=C-Reactive Protein.*

Variables	Sepsis with acute kidney injury		p	Sepsis with acute kidney injury		p
CRP Level (mg/dl)	Shock	Non-Shock		Shock	Non-Shock	
Mean	47.3	63.57	0.09	51.47	55.7	0.36
Standard Deviation	65.19	43.91		66.91	51.96	
Median	37.2	67.25		18.5	44.5	
Minimum	0.1	8		1	1.2	
Maximum	265.2	140		199.6	160.9	

Table 4. *Relationship between AKI and Length of Stay in PICU in pediatric sepsis patients, p=Mann-Whitney; PICU=Pediatric Intensive Care Unit; SD=Standart deviasion.*

Acute Kidney Injury	Length of Stay in PICU (Days)					n	p
	Mean	SD	Median	Minimum	Maximum		
Yes	10.05	5.63	10.5	1	21	36	0.25
No	8.61	4.46	7.5	3	19	54	

Table 5. *Relationship between AKI stage based on pRIFLE criteria with shock in septic children, p=Kolmogorov-Smirnov; AKI=Acute Kidney Injury, *p=Kruskal-wallis test; Post Hoc Mann-Whitney test: Risk vs injury P=0.141, Risk vs Failure p= 0.360, Injury vs Failure p=0.00; AKI=Acute Kidney Injury; PICU=Pediatric Intensive Care Unit, SD=Standard Deviation.*

Variables	Shock		p	Length of Stay in PICU		p*
	Yes n (%)	No n (%)		Mean (SD)	Median (Min-Max)	
AKI Stage			0.54			0.01
Risk	6 (60)	4 (40)		10.50 (6.34)	11.00 (2-19)	
Injury	6 (75)	2 (25)		15.25 (4.59)	15.00 (6-21)	
Failure	16 (88.89)	2 (11.11)		7.50 (3.95)	6.00 (1-16)	

Failure stage according to the pRIFLE criteria. Out of the 10 children who had AKI Risk stage, there were 6 children who experienced shock and 2 children. Out of the 8 children with AKI stadium Injury, 6 children experienced shock and 2 children did not. Out of the 16 children with AKI Failure stage, 16 children experienced shock and 2 children did not experience shock. With the Kolmogorov-Smirnov statistical test to determine the relationship between AKI stage and the incidence of shock, it was found that there was no significant difference with the value of p=0.54.

When compared between the incidence of AKI and no AKI in relation to length of stay there was no statistically significant difference; but after being compared between each stage using the Kruskal-Wallis statistical test, a significant difference was found between the length of stay between stages of AKI with a value of P=0.01 as seen in Table 5. Children with Risk stage have a median of 11 days hospitalization with a range of 2-19 days, median injury 15 days with a range of 6-21 days and Failure stage with a median of 6 days with a range of 1-16 days. By carrying out the Post-Hock test using the Mann-Whitney test, it was found that significant differences were obtained compared to the length of stay between children with AKI Injury stage and Failure stage with a value of p=0.00 whereas compared to the length of stay in PICU between Risk stage and Injury stage and Risk stage and Failure stage, there were no significant differences in terms of hospitalization with p=0.14 for Risk stage compared to injury stage and p=0.36 for Risk stage compared to Failure stage.

Patients with sepsis who have AKI and shock have an average hospitalization of 9.14 days, median of 8.00 days with a range of 1.00-20.00 days. Patients with sepsis who had AKI but did not experience shock had a hospital stay of 13.35 days, a median of 13.50 days with a range of 5.00-21.00 days. Patients with sepsis who did not have AKI but suffered shock had a mean hospitalization of 6.37 days, a median of 5.50 days with a range of 3.00-13.00 days and lastly septic patients who did not have AKI and also did not have an average hospitalization of 10, 40 days, median 9.50 days with a range of 3.00-19.00 days. Using the Kruskall-Wallis statistical test, it was found that there was at least one significant relationship when compared to the length of stay of patients who had AKI or no AKI if accompanied by shock or no shock with a value of p = 0.03. Post Hoc tests using the Mann-Whitney test found that statistically significant differences were found when compared to length of stay between: (a) septic patients who had AKI and shock with septic patients who had AKI but did not experience shock with a value of p=0.03, (b) sepsis sufferers who have AKI but do not Shock with patients with sepsis without AKI but experience Shock with a value of p=0.01, and (c) patients with sepsis without AKI but Shock with patients with sepsis

without AKI and not experiencing shock with a value of p=0.00.

Discussion

Children with critical illness have a greater chance to experience AKI. Around 5-12% of children treated in ICU experience AKI with various degrees.8 Most recently, a meta-analysis involving 154 studies of more than 3,000,000 people revealed that one in five adults and one in three children worldwide experienced AKI during one period of hospital care [9]. Some researchers found that the incidence of AKI in pediatric patients with critical illness ranged from 4.4% - 54.5% with sepsis as the main cause [8,10-12].

From this study it was found that the most common source of infection causing sepsis was from the respiratory tract of both Community acquired pneumonia and pulmonary tuberculosis (total 56.6%), then from the nervous system in the form of tuberculous meningitis, encephalitis and meningitis with a total of 23.3%, urinary tract infection 5.6%, gastrointestinal tract infection 3.3%. The SPROUT study (Sepsis Prevalence Outcome and Therapies) by Weiss et al. [16] Involving 126 hospitals from 26 countries also found that the most infections in sepsis were in the respiratory system (40%).

Sepsis is the most common cause of AKI in critically ill patients. Naik et al. [10] Found that of 252 children who were critically ill and treated in PICU, 103 children (40.9%) had AKI with details of 39 children having AKI Risk stage, 37 children had AKI Injury stage and 27 have AKI Failure stage. One cohort study in Brazil also found that the incidence of AKI in PICU patients was 46% with the percentage of each stage being 38.1%, 36.2%, and 17.2% for risk, injury, and failure [17].

In this study there were no significant differences in sex between the two groups of children with sepsis who had AKI. The same results were obtained by Bresolin [18] et al., Naik et al. [10] and Wong's et al. [19] also found that sepsis non-survivors and survivors were not significantly different between men and women. The same results were also found in a study conducted by Bozza [17] in Brazil, and Runtunuwu [20] in Manado.

Based on nutritional status, there was no significant difference between children with normal nutritional status and malnutrition in terms of sepsis and also AKI cases due to sepsis in patients treated in PICU with. However, in patients with AKI or shock it appears that the proportion of malnourished children is greater than children with normal nutritional status. This is similar to a study by Menezes et al. [21] Malnutrition causes changes in systemic function including reduced immune response, atrophy and increased permeability of the intestinal mucous barrier which facilitates infection and bacterial translocation. It will increase the incidence of pneumonia, sepsis and other conditions that can trigger increased mortality, length of stay and cost of care.

Statistically, there was no significant difference in age between the two groups in septic patients. Runtunuwu [20] also reported statistically no significant differences were found between sepsis sufferers and sepsis shock based on subject age. In the larger population of children and adolescents, the age factor does not significantly influence the incidence of septic shock and it can explain the meaningless age factor for the occurrence of septic shock.

There was no significant difference between patients with AKI and shock with AKI patients but did not experience shock. Whereas among sepsis patients induced AKI but shock when compared with septic patients without AKI and shock also did not differ significantly. CRP plays an important role in the innate immune response and is known to be one of the inflammatory markers. Non-inflammatory individuals usually have CRP levels <1 mg/ L. CRP levels can increase to 100 times the normal value in cases of acute inflammation, such as infection, trauma, and malignancy. Meanwhile, CRP levels will decrease if the inflammatory process in the body has been completed. So that the inflammatory process can be seen from the CRP values that are serially examined in septic patients. This difference in results can be caused because the sample of this study only took septic patients who generally had CRP levels that were more than normal. In addition, the assessment of CRP levels in the sample of this study was not done serially.

In this study, it was found that there were significant differences in the incidence of shock between children with sepsis who had AKI and those who did not have AKI. Children with AKI due to sepsis have 4.37 times more risk to experience shock compared to children with sepsis without AKI. Similar results were obtained by Bresolin et al. [18] The pathophysiology of septic shock is not yet fully understood, but is suspected to involve complex interactions between the pathogen and the host's immune system. Normal physiological responses to local infections include activation of the host defence mechanism which results in neutrophil and monocyte influx, release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of the coagulation pathway [22]. Sepsis is a well-known risk factor in the incidence of AKI, occurring in about 19% of septic patients, 23% in patients with severe sepsis, and 51% of patients with septic shock. At present, the pathophysiology of AKI due to sepsis is multifactorial including changes and disturbances in glomerular filtration pressure and in the intrarenal distribution of blood flow, inflammation, oxidative stress, apoptosis, microcirculation disorders, mitochondrial dysfunction, and inter-organ communication [23]. From experimental studies, it was shown that GNGA was able to induce functional changes in immune cell responses and in leukocyte adhesion and leukocyte extravasation both in the kidneys and in the heart which could cause myocyte apoptosis [24]. In a cross-sectional study in AKI patients also showed increased levels of High Mobility Group Box 1 (HMBG1). HMBG1 released into extracellular fluid acts as DAMP which mediates the inflammatory response and can increase the risk of shock [15]. If kidney function is interrupted by any cause, the kidneys will not be able to maintain normal physiological functions. It is characterized by physiological changes that affect heart problems. These include: oliguria, electrolyte imbalance, acidemia, and also uremic toxin build up. This disorder can increase the risk of cardiovascular disorders and cause shock [16].

Furthermore, with post Hock test found that the difference was obtained when compared to the length of treatment between AKI Injury stage patients and Failure stage. The same thing was stated by Bresolin et al. [18], but he did not give comparison between stages [25].

Conclusion and Limitations

Previous studies on Acute Kidney injury were about sepsis and non-sepsis admitted to PICU, hence, this study was designed to limit the bias of the non-sepsis incidence. Meanwhile, the limitation of this study is the parameter use was length of stay in the PICU, which can be affected by patient survival and also other factor such as, discharge against medical advice or the underlying disease).

Incidence of sepsis-induced AKI in this cohort of children was 40%, and shock severity in patients with sepsis induced-AKI was higher than those with sepsis without AKI, and there was no difference in length of stay between sepsis patients with AKI and without AKI.

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Correspondence to:

Idham Jaya Ganda
Department of Pediatrics,
Faculty of Medicine, Hasanuddin University,
Makassar, South Sulawesi,
Jl. Perintis Kemerdekaan Km. 10 Tamalanrea
Makassar, 90245, Indonesia
Tel: 62411- 584461, Fax: 62411- 590629
E-mail: dhamjaya_spa@yahoo.com