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Original Article

Risk factors for acute kidney injury in children with critical illness

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Abstract

Background Acute kidney injury (AKI) is an acute functional kidney disorder that increases morbidity and mortality in children. The mortality rate for critically ill patients accompanied by AKI is quite high and is influenced by the degree of AKI, the severity of the disease, and organ function disorders. Understanding the risk factors of developing AKI in children with critical illness can help prevent AKI.

Objective To determine the risk factors for AKI in children with critical illness.

Methods This retrospective cohort study included 255 children aged 1 month to 18 years admitted at the pediatric intensive care unit (PICU) of dr. Zainoel Abidin Regional Public Hospital, Banda Aceh, Aceh, from January to December 2022 using medical record data. Bivariate and multivariate analyses were performed.

Results Acute kidney injury occurred in 68 (26.7%) patients. Based on pRIFLE criteria, 34 (50%) patients had AKI in the failure stage. Risk factors for AKI in children with critical illness were in descending order of RR: sepsis (RR 14.3; 95%CI 11.68 to 18.66; P=0.000), mechanical ventilation (RR 12.13; 95%CI 8.75 to 15.98; P=0.000), respiratory disorders (RR 2.51; 95%CI 2.06 to 4.02; P=0.003), congenital heart disease (RR 2.08; 95%CI 2.00 to 3.05; P=0.004), CNS disorders (RR 1.24; 95%CI 1.02 to 2.49; P=0.048), nephrotoxic drug use (RR 1.41; 95%CI 1.24 to 3.08; P=0.000), and age 1 month to 5 years (RR 0.072; 95%CI 0.16 to 0.32; P=0.010).

Conclusion Sepsis is a risk factor for AKI in children with critical illness, followed by mechanical ventilation use, respiratory disorders, nephrotoxic drug use. Age <5 years is a protective factor . **[Paediatr Indones. 2024;64:398-404; DOI: https://doi.org/10.14238/pi64.5.2024.398-404].**

Keywords: *acute kidney injury; determinant risk factors; children; critical illness*

Acute kidney injury (AKI) is a sudden-onset disorder affecting kidney function, leading to imbalances in fluid and electrolytes. It also contributes to increased morbidity and mortality among critically ill children.[1,2] Currently, there are several criteria for establishing an AKI diagnosis, such as pRIFLE and *Kidney Disease Improving Global Outcomes* (KDIGO).[3] The pRIFLE system categorizes the diagnosis of AKI in children into three severity levels (risk, injury, failure) and includes two outcome variables (loss and end-stage renal disease/ESRD). On the other hand, the KDIGO criteria classify AKI diagnosis based on three levels of severity determined by serum creatinine values and urine output.[4]

Epidemiological studies conducted by the Assessment of *Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology* (AWARE) in 31 countries in 2016 revealed that, based on the pRIFLE criteria, the AKI incidence was 26.9% in 4,683 critically ill children treated in the PICU. According to the KDIGO criteria,

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11.6% of children developed incident AKI stage 2 or 3 within 7 days of treatment.[3,5] Several studies have reported that children with AKI experience extended PICU stays, necessitate mechanical ventilation, and are at risk of progressing to chronic kidney disease. Therefore, a primary focus for children with critical illness should be the prevention and early detection of AKI to enhance prognosis.[6]

Two previous studies also identified risk factors that can influence the development of AKI, including age, shock, sepsis, congestive heart failure, and the use of nephrotoxic drugs.[7,8] Multivariate analysis revealed that age, sepsis, shock, and high *Pediatric Risk of Mortality* (PRISM) score are included as risk factors for acute kidney injury. Nephrotoxic drug use as the main risk factor for AKI in children.[9] Epidemiological studies showed that sepsis increases the incidence of AKI, according to the severity, with 11-60% in sepsis patients, 23% in severe sepsis patients, and 51-64% in septic shock patients.[10] Sepsis causing AKI was associated with higher risk of death and hospital mortality rates. AKI has an overall mortality rate of 45%, while the mortality rate for AKI caused by sepsis is more than 70%.[11]

This study was aimed to determine the risk factors for AKI in children with critical illness.

Methods

This analytical observational study with a retrospective cohort design used a total sampling method. Sampling was done from PICU patient medical record data from January to December 2022. Inclusion criteria were critically ill pediatric patients aged 1 month-18 years with nutritional status normal, undernutrition, malnutrition, overweight, and obesity. The sampling was had complete medical record data. The exclusion criteria were patients with pre-existing acute and chronic kidney disease, kidney replacement therapy, treatment <24 hours, atypical progressive acute kidney disease , or congenital kidney abnormalities. There were 255 patients with critical illness were collected to study the risk factors for AKI in children with critical ill. This study was approved by the Health Research Ethics Committee of the Dr. Zainoel Abidin Regional Public Hospital, Banda Aceh. The data were analyzed using bivariate analysis with the Chi-square and Fisher's tests, and multivariate analysis by logistic regression analysis using SPPS software. The level of significance used in this study was $P<0.05$.

Results

Of 255 children who met the inclusion criteria for critical illness, 68 (26.7%) patients had AKI and 187 (73.3%) patients did not have AKI. Most critically ill children with AKI were males (55.9%) aged 1 month to 5 years with undernutrition (45.6%), as shown in **Table 1**.

Based on the pRIFLE criteria, the most common grade of AKI was failure stage in 34 (50%) patients, as shown in **Table 2**. The most common primary

Table 1. Basic characteristics of study subjects

Basic characteristics	Critical illness	
	AKI (n=68)	Non-AKI (n=187)
Gender, n (%)		
Male	38 (55.9)	96 (51.3)
Female	30 (44.1)	91 (48.7)
Age, n (%)		
1 month-5 years	43 (63.2)	60 (32)
5-10 years	13 (19.1)	78 (41.7)
10-18 years	12 (17.7)	49 (26.3)
Nutritional status, n (%)		
Normal	21 (30.9)	75 (40)
Undernutrition	31 (45.6)	65 (34.8)
Malnutrition	10 (14.7)	23 (12.3)
Overweight	3 (4.4)	19 (10.2)
Obesity	3 (4.4)	5 (2.7)

Table 2. Clinical characteristics of study subjects

Clinical characteristics	AKI (n=68)	Non-AKI (n=187)
AKI degree, n (%)		
Risk	13 (19.1)	-
Injury	21 (30.9)	-
Failure	34 (50)	-
Primary disease, n (%)		
Respiratory disorders	26 (38.2)	54 (28.9)
Congenital heart disease	10 (14.7)	9 (4.8)
CNS disorders	16 (23.5)	40 (21.4)
Post-surgery	7 (10.3)	45 (24)
Gastrointestinal infection	4 (5.9)	8 (4.3)
Dengue infection	2 (2.9)	15 (8)
Malignancy	1 (1.5)	11 (5.9)
Endocrine disease	2 (3)	5 (2.7)
Mechanical ventilation use, n (%)		
Yes	63 (92.6)	63 (33.7)
No	5 (7.4)	124 (66.3)
Nephrotoxic drug use, n (%)		
Yes	9 (13.2)	0 (0)
No	59 (86.8)	187 (100)
Respiratory failure, n (%)		
Yes	63 (92.6)	63 (33.7)
No	5 (7.4)	124 (66.3)
Sepsis, n (%)		
Yes	61 (89.7)	47 (25.1)
No	7 (10.3)	140 (74.9)
Shock, n (%)		
Sepsis	43 (63.2)	47 (25.1)
Other causes	25 (36.8)	140 (74.9)
PELOD-2 score, n (%)		
≥10	57 (83.8)	46 (24.6)
<10	11 (16.2)	141 (75.4)
Duration of hospitalization, n (%)		
<3 days	5 (7.4)	17 (9)
≥3 days	63 (92.6)	170 (91)

disease in the AKI group was respiratory disorders in 26 (38.2%) patients, followed by disorders of the central nervous system (CNS) in 16 (23.5%) patients and congenital heart disease in 10 (14.7%) patients.

Most pediatric patients treated for AKI experienced respiratory failure and used mechanical ventilation (63 patients; 92.6%). Most of the AKI patients had sepsis (61; 89.7%), as well as septic shock (43; 63.2%). Fifty-seven (83.8%) patients had PELOD-2 scores ≥10. All patients who used nephrotoxic drugs had AKI (9; 13.2%), as explained in **Table 2**. Length of stay for pediatric patients with critical illness treated in the PICU at RSUD Dr. Zainoel Abidin during the research period was mostly more than 3 days, as much as 91.3%.

As shown in **Table 3**, children aged 1 month-5 years had 2.01 times higher risk of AKI. Gender and nutritional status had no significant association with the incidence of AKI.

The most common primary disease in the AKI group was respiratory disorders in 26 (38.2%) subjects; those with respiratory diseases had a 1.27 times higher risk of AKI than those with non-respiratory disorders, as shown in **Table 4**. Mechanical ventilation use and respiratory failure both increased the risk of AKI by 12.9 times. All subjects who used nephrotoxic drugs had AKI (9; 13.2%). Use of this medication had a 4.16 times higher risk of AKI in critically ill children than those who did not take such drugs. Sepsis (61; 89.7%) and shock (43; 63.2%) occurred most frequently

Table 3. Analysis of subjects baseline characteristics and AKI in critical illness

Baseline characteristics	Critical illness		RR	95% CI	P value
	AKI (n=68)	Non-AKI (n=187)			
Gender, n(%)			1.14	0.75 to 1.72	0.52
Male	38 (55.9)	96 (51.3)			
Female	30 (44.1)	91 (48.7)			
Age, n(%)			2.01	1.35 to 2.98	0.00
1 month-5 years	43 (63.2)	60 (32.0)			
5-10 years	13 (19.1)	78 (41.7)			
10-18 years	12 (17.7)	49 (26.3)			
Nutritional status, n(%)			0.96	0.72 to 1.27*	0.31
Normal	21 (30.9)	75 (40.0)			
Undernutrition	31 (45.6)	65 (34.8)			
Malnutrition	10 (14.7)	23 (12.3)			
Overweight and obesity	6 (8.8)	24 (12.9)			

*Chi-square analysis

Table 4. Analysis of subject clinical characteristics and AKI in critical illness

Clinical characteristics	Critical illness		RR	95% CI	P value
	AKI (n=68)	Non-AKI (n-187)			
Primary disease, n(%)			1.27	1.06 to 1.52*	0.013
Respiratory disorders	26 (38.2)	54 (28.9)			
Congenital heart disease	10 (14.7)	9 (4.8)			
CNS disorders	16 (23.5)	40 (21.4)			
Post-surgery	7 (10.3)	45 (24.0)			
Gastrointestinal and dengue infections	6 (8.8)	23 (12.3)			
Endocrine malignancies and diseases	3 (4.5)	16 (8.6)			
Mechanical ventilation, n(%)			12.9	5.36 to 31.0	0.00
Present	63 (92.6)	63 (33.7)			
Not present	5 (7.4)	124 (66.3)			
Nephrotoxic drugs, n(%)			4.16	3.33 to 5.20**	0.00
Present	9 (13.2)	0			
Not present	59 (86.8)	187 (100)			
Respiratory failure, n(%)			12.9	5.36 to 31.0	0.00
Yes	63 (92.6)	63 (33.7)			
No	5 (7.4)	124 (66.3)			
Sepsis, n(%)			11.86	5.65 to 24.9	0.00
Sepsis	61 (89.7)	47 (25.1)			
Not sepsis	7 (10.3)	140 (74.9)			
Shock, n(%)			3.1	2.07 to 4.80	0.00
Sepsis	43 (63.2)	47 (25.1)			
Other causes	25 (36.8)	140 (74.9)			
PELOD-2 score, n(%)			1.3	0.7 to 2.3	0.00
≥10	57 (83.8)	46 (24.6)			
<10	11 (16.2)	141 (75.4)			
Duration of hospitalization, n(%)			0.82	0.37 to 1.86	0.66
<3 days	5 (7.4)	17 (9.0)			
≥3 days	63 (92.6)	170 (91.0)			

*Chi-square analysis **Fisher's test analysis

in the AKI group. Sepsis subjects had 11.86 times higher risk of AKI and shock due to sepsis had 3.1 times higher risk of AKI. PELOD-2 score ≥10 had a relative risk of 1.3 for AKI. Hospital length of stay was not a significant risk factor for AKI in children with critical illness.

Multivariate analysis with logistic regression was performed to determine risk factors for AKI in children with critical illness. Eight variables were included in the analysis: age 1 month to 5 years, primary disease, mechanical ventilation, nephrotoxic drug use, respiratory failure, sepsis, shock etiology, and PELOD-2 score ≥10, as shown in **Table 5**. Multivariate analysis revealed that the following risk factors for AKI in children with critical illness maintained their significance: sepsis, mechanical ventilation, primary disease of respiratory disorders, nephrotoxic drug use. Age 1 month to 5 years showed as a protective factor (RR<1).

Discussion

Of the 255 subjects, there were more males (55.9%) than females (44.1%). This result similar to a study reported 447 children treated in the Cerrahpasa PICU, Turkey, where AKI was more common in boys than girls.[11]

The degree of AKI identified in our subjects based on pRIFLE criteria was mostly in the failure stage at 50%, followed by the injury stage at 30.9%, and the risk stage at 19.1%. This result was in agreement with a study which noted that of 77 children with sepsis and AKI who were treated in the PICU of level 3 hospitals in Mexico in 2016, failure-stage AKI was more common in pediatric patients with critical illness compared to injury stage AKI.[13] Kidneys are the target organ of bacterial caused sepsis in children with critical illness and sepsis. Initially, the kidneys typically maintain good function in sepsis, but sepsis progression leads to an increased inflammatory response, reducing kidney function.[7]

Bivariate analyses revealed a significant association between age of 1 month to 5 years and the incidence of AKI in children with critical illness. A Chine study reported that in 127 children with sepsis in the PICU of Anhui Children's Hospital of China in May 2015-May 2018, the incidence of AKI was influenced by age 1 month to 5 years, underlying disease, and source of infection.[14] Children under 5 years old have immature immune systems, which makes them more susceptible to serious infections and sepsis.[12]

The primary disease as the main cause of AKI in children with critical illness in this study were respiratory disorders with RR 2.51 (95% CI 2.06 to 4.02), congenital heart disease with RR 2.08 (95% CI 2.00 to 3.05), and CNS disorders with RR 1.24 (95% CI 1.02 to 2.49), Similarly, a previous study reported that the most common primary disease in critically ill patients with AKI was respiratory system problems such as pneumonia.[15] A combination of environmental factors and airborne pathogens can lead to infections of the airways. These pathogens can also cause adhesions and migration of pro-inflammatory cytokines to the blood vessels.[9]

Mechanical ventilation was associated with the incidence of AKI in children with critical illness (RR 12.9; 95%CI 5.36 to 31.0; P=0.000). This finding aligns with a study which showed that mechanical ventilation had a 3 times increased risk of AKI in children with critical illness.[16] Mechanical ventilation

Table 5. Multivariate analysis with logistic regression of possible AKI risk factors in children with critical illness

Variables	RR	95% CI	P value
Age 1 month-5 years	0.72	0.16 to 0.32	0.010
Primary disease			
Respiratory disorders	2.51	2.06 to 4.02	0.003
Congenital heart disease	2.08	2.00 to 3.05	0.004
CNS disorders	1.24	1.02 to 2.49	0.048
Mechanical ventilation	12.13	8.75 to 15.98	0.000
Nephrotoxic drug use	1.41	1.24 to 3.08	0.000
Respiratory failure	1.24	0.73 to 2.08	0.320
Sepsis	14.3	11.68 to 18.66	0.000
Shock	2.6	0.67 to 10.3	0.160
PELOD-2 score ≥10	3.51	0.57 to 21.43	0.170

likely causes hemodynamic disturbances and renal vasoconstriction due to sympathetic stimulation.[16]

Sepsis was a significant risk factor for AKI (RR 14,3; 95%CI 11.68 to 18.66; P=0.000). Another study also reported that sepsis was a risk factor for AKI in children with critical illness, with RR 4.3 (95%CI 0.93 to 19.78) and they also found increased mortality in sepsis patients accompanied by AKI.[12] Sepsis may increase the risk of AKI due to systemic vasodilation and systemic hypotension, leading to disturbances in glomerular filtration pressure and intrarenal distribution of renal blood flow, afferent and efferent arterial vasodilation, as well as microcirculation disorders. Then the hypoxic-ischemic conditions cause the AKI.[15]

Nephrotoxic drugs such as aminoglycosides, chemotherapy agents, non-steroid anti-inflammatory drugs (NSAIDs), and antimicrobials were a significant risk factor for AKI in children with critical illness (RR 1.41; 95%CI 1.24 to 3.08; P=0.000). Various types of drugs, such as antimicrobials, ACE inhibitor agents, chemotherapy agents, and NSAIDs, have been shown to play a role in drug-induced kidney damage.[17] Mechanisms of drug induction include prerenal hypoperfusion, intrinsic renal damage, renal tubular obstruction, and damage to the renal microvascular structure.[9]

The limitations of our study were the retrospective study design, and holding the study in only one hospital, so that we cannot generalize our findings to represent all children with critical illness accompanied by AKI. In addition, the diagnosis of AKI was based only on an increase in serum creatinine and glomerular filtration rate.

In conclusion, the significant risk factors for AKI in children with critical illness are sepsis, mechanical ventilation, respiratory disorders, nephrotoxic drug use. Age less than 5 years is a protective factor.

Conflict of interest

None declared.

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