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Original Article

Neutrophil lymphocyte ratio and severity of acute kidney injury in septic children

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Abstract

Background Acute kidney injury (AKI) in sepsis is associated with an inflammatory process in kidney microcirculation and may increase morbidity and mortality in children. The neutrophil lymphocyte ratio (NLR) is an inflammatory biomarker of the inflammatory process in sepsis.

Objective To determine the role of NLR in predicting the severity of AKI and to describe the demographic and laboratory characteristics, as they relate to outcomes of pediatric patients with AKI and sepsis.

Methods This cross-sectional study was conducted in the PICU at Dr. Zainoel Abidin General Hospital (RSUDZA), Banda Aceh, Aceh. Medical record data were obtained from critically ill children with sepsis and AKI. Chi-square test was used to compare the proportions of each variable. We also calculated odds ratios to evaluate the AKI severity, PELOD-2 score, and patient outcomes. Spearman's analysis was used to look for a possible correlation between NLR and AKI severity in septic children.

Results Seventy-one subjects with sepsis and AKI were included. Subject characteristics were as follows: 63.4% males, 63.4% < 1 year of age, 56.3% with respiratory problems as a primary disease, 38% with AKI injury stage, and 54.9% subjects with PELOD-2 score ≥10. There was no significant correlation between AKI severity and mortality (OR 3.04; 95%CI 0.990 to 9.378; P=0.052). Subjects with a PELOD-2 score ≥10 had a 47.6 times higher chance of mortality in septic children with AKI compared to those with PELOD-2 scores <10. There was no correlation between NLR and AKI severity (r=0.019; P=0.878).

Conclusion There is no correlation between NLR and AKI severity. Sepsis accompanied by AKI may increase the risk of mortality in children. Septic children with more severe AKI tends to be less survive. **[Paediatr Indones. 2023;63:492-8; DOI: https://doi.org/10.14238/pi63.6.2023.492-8**].

Keywords: *sepsis; acute kidney injury; neutrophil-lymphocyte ratio; pelod-2 score; children; mortality*

Sepsis is a life-threatening condition derived from a systemic blood infection that can damage one or more organs due to dysregulation of the immune response.[1] Sepsis and septic shock are potential causes of morbidity and mortality in children treated in hospital wards and intensive care units (ICUs). The incidence of sepsis is higher in newborns and babies <1 year of age than among children aged 1 to 18 years.[2] There are an estimated 22 cases of children with sepsis per one million live births and 2,202 cases of neonates with sepsis per one million live births worldwide.[3] Sepsis affected 19.3% of 502 patients treated in the PICU at Dr. Cipto Mangunkusumo Hospital (RSCM) at 2012 until 2016, with a death rate of 54.0%.[4]

Acute kidney injury (AKI) is a frequent sepsis complication associated with increased mortality, morbidity, hospital length of stay, and patient treatment costs. The incidence of AKI in patients with septic shock was reported to be 48%, with

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the highest at 68% in the PICU.[5] The AKI is a risk factor for poor outcomes and occurs in approximately one-third of children with septic shock. In the *Sepsis Prevalence Outcomes and Therapies Study*, 21% of sepsis patients were found to have stage 2/3 AKI, which was associated with an increased risk of death or disability.[6] Several factors contribute to AKI, including ischemic-reperfusion injuries, direct inflammatory injuries, endothelial cell abnormalities, clotting, and apoptosis.[7] The pathophysiology of sepsis leading to AKI is not fully understood.[8]

Acute kidney injury is diagnosed based on functional indicators, such as serum creatinine, due to the patient's unstable condition.[7] However, serum creatinine level is insufficient for diagnosing renal injury and recovery. White blood cell (WBC) count is more revealing, as these cells are crucial to the systemic inflammatory response in severe infection, trauma, or shock. Neutrophils, lymphocytes, monocytes, eosinophils, and basophils, are the types of leukocytes that can be differentiated through complete blood testing.[9] Neutrophils are the initial leukocytes that migrate from the circulation to the site of an injury or illness in order to eradicate harmful microorganisms and cellular debris. The immunological response to endotoxins increases the neutrophils and decreases the lymphocytes.[10] Neutrophil-lymphocyte ratio (NLR) is a biomarker of systemic inflammation. It is readily available and simple to calculate from a complete blood count.[11] The NLR indicates a balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. Prior study has demonstrated that high NLR is connected to elevated amounts of several pro-inflammatory cytokines, causing DNA damage to cells.[12] NLR can predict cardiovascular mortality, survival in malignancies, surgical outcomes, and the advancement of chronic kidney disease (CKD). At the level of the kidney tissue itself and systemically, inflammation plays a role in AKI pathophysiology; NLR, as a marker of inflammation, can predict the development of AKI.[13]

Neutrophil-lymphocyte ratio has been used as a prognostic marker in patients with bacterial infections. The NLR can predict the development of AKI in patients with severe sepsis, with a 90.7% sensitivity and 92.9% specificity.[13] Moreover NLR was a significant predictor of the incidence of AKI.[14] Earlier studies have shown that NLR values can predict the development of AKI in severe sepsis patients, but mostly in adult subjects.[12,13,15,16] More studies on NLR and its relationship to AKI severity are needed in children. Thus, we aimed to investigate for an association between NLR and AKI severity in pediatric patients with sepsis.

Methods

This cross-sectional study was done to evaluate for a possible correlation between NLR and AKI severity in children with sepsis in the PICU at Dr. Zainoel Abidin Regional Public Hospital (RSUDZA), Banda Aceh, Aceh. Subjects were included by total sampling. We collected data on subject characteristics, laboratory results, and outcomes of pediatric patients with sepsis and AKI from the medical records of RSUDZA, Banda Aceh.

Subjects aged 1 month to 18 years, admitted to the PICU at RSUDZA with a diagnosis of sepsis and AKI, and had complete medical record data, were included in this study. Patients with primary renal disease, chronic renal disease persisting for more than three months, and/or hematological disorders, were excluded from the study. AKI is determined in children based on the amount of urine produced and/or a decrease in glomerular filtration rate, calculated by the Schwartz formula. It is referred to as AKI risk when the glomerular filtration rate (GFR) decreased by 25%, AKI injury when the GFR decreased by 50% from average, and AKI failure when the GFR decreased by 75%.[17] The Emergency and Pediatric Intensive Care Division confirmed the diagnosis of sepsis, and Pediatric Nephrology Division of RSUDZA confirmed the diagnosis of AKI using pRIFLE criteria.

Univariate analysis was used to determine the frequency distribution of each variable. Descriptive statistics results showed the frequency, distribution, and percentage of subject characteristics. Chi-square test was used to analyze severity of AKI, PELOD-2 score, and patient outcomes. Mantel-Haenszel technique was used to estimate odds ratios between AKI severity, PELOD-2 score, and patient outcomes. Spearman's test was used for correlation analysis, with the ANOVA linearity test previously conducted. Data analysis was performed using *SPSS 26.0 for Windows* software (*IBM*, Armonk, New York). This study was

approved by the Ethics Committee of Universitas Syiah Kuala Medical School/Dr. Zainoel Abidin Hospital Banda Aceh.

Results

We initially screened 127 medical records of pediatric sepsis patients hospitalized in the PICU, Dr. Zainoel Abidin Hospital, Banda Aceh, between January and December 2020. Of 98 individuals with sepsis, only 71 medical records met the inclusion criteria. Of the 71 subjects, 45 (63.4%) were male, 24 (33.8%) were <1 year of age, 34 (47.9%) had good nutrition, 40 (56.3%) had respiratory problems as a primary disease, 39 (54.9%) had a PELOD-2 score ≥ 10, and 38 (53.5%) reportedly died (**Table 1**). **Table 2** shows the AKI severity in in subjects at the time of admission: 27 (38%) subjects had AKI injury stage and 26 (36.6%) subjects had AKI failure stage.

Subjects had a median WBC count of 17.2x10^3/mm^3. The medians for banded neutrophils, segmented neutrophils, and lymphocytes were 0%, 76%, and 12%, respectively. The median NLR, ureum, and creatinine were 6.42, 36 mg/dL, and 1.1 mg/dL, respectively. As shown in **Table 3**, the mean percentage reduced GFR value of AKI stages in injury and failure were 63.94 (SD 8.21)% and 86.6 (SD 6.95)%, respectively.

In our study, 38 (53.5%) sepsis patients with AKI died, most of whom had either AKI injury or failure stage. The 39 subjects with a PELOD-2 score of ≥10 had worse outcomes than those with PELOD-2 score

Table 1. Basic characteristics of subjects with sepsis and AKI

Characteristics	(N = 71)
Age group, n (%)	
< 1 year	24 (33.8)
1-5 years	14 (19.7)
5-10 years	7 (9.9)
10-13 years	7 (9.9)
13-18 years	19 (26.8)
Gender, n (%)	
Male	45 (63.4)
Female	26 (36.6)
Nutritional status, n (%)	
Good nutrition	34 (47.9)
Malnutrition	22 (31.0)
Severe acute malnutrition	6 (8.5)
Overweight	7 (9.9)
Obesity	2 (2.8)
Primary diseases, n (%)	
Central nervous system	24 (33.8)
Respiratory	40 (56.3)
Cardiovascular	2 (2.8)
Endocrine	2 (2.8)
Surgical	3 (4.2)
PELOD-2 score, n (%)	
<10	32 (45.1)
≥10	39 (54.9)
Outcomes, n (%)	
Survived	33 (46.5)
Died	38 (53.5)

Table 2. Severity of AKI in septic children

Severity of AKI, n (%)	(N= 71)
Risk	18 (25.5)
Injury	27 (38.0)
Failure	26 (36.6)

Table 3. Subjects' laboratory values

Laboratory value	(N=71)
Median WBC (range), x10^3/mm^3	17.2(1.1-80.92)
Median banded neutrophils (range), %	0 (0-1)
Median segmented neutrophils (range), %	76 (45-89)
Median lymphocytes (range), %	12 (4-46)
Median NLR (range)	6.4167 (0.98-22.25)
Median ureum (range), mg/dL	36 (4-353)
Median creatinine (range), mg/dL	1.1 (0.4-12.5)
Median decreased GFR (range), %	70.38 (10.66-96.96)
Mean decreased GFR of AKI risk (SD)	36.14 (11.85)
Mean decreased GFR of AKI injury (SD)	63.94 (8.21)
Mean decreased GFR of AKI failure (SD)	86.64 (6.95)

of <10. **Table 4** shows the analysis of AKI severity and PELOD-2 score. Subjects with AKI injury and failure had 3.04 times the risk of death than those with AKI risk, but the correlation was not significant (OR=3.04; P=0.052). PELOD-2 score ≥10 increased the risk of mortality by 47.6 times compared to a PELOD-2 score <10 (OR=47.6; P< 0.001).

Table 5 shows the mean NLRs for AKI risk [7.08 (SD 4.50)], AKI injury [7.14 (SD 4.51)], and AKI failure [6.99 (SD 4.29)]. There were no significant correlations between NLR and AKI severity, as shown in Table 5 (P>0.05 for risk, injury, and failure).

Discussion

We analyzed NLR and AKI severity in septic children treated in the PICU. Subjects were predominantly males. A study also reported that septic children were predominantly male.[18] Females reportedly have a stronger humoral immune response than males, as evidenced by higher immunoglobulin levels and superior immunoglobulin production after vaccination.[19] Due to a considerable increase in pro-inflammatory mediators, such as TNF-, IL-6, and IL-10, males experience more severe sickness, whereas females have a higher concentration of anti-inflammatory mediators.[13]

Sepsis incidence was higher in children aged <1 year. The incidence of sepsis is influenced by age, underlying conditions, and infection source.[20,21] Children under five have immature immune systems, thus they are more likely to get serious infections or even sepsis.[22]

In our study, respiratory illness was the primary disease leading to organ dysfunction in septic children. In agreement with this finding, a study in Palembang, South Sumatera, noted that 58.3% of sepsis etiologies were pneumonia.[23] Another study also found that respiratory problems were the primary disease in sepsis patients with AKI complications.[24] Environmental factors and airborne pathogens can cause airways to be more prone to infection.[25]

In our subjects, AKI in the injury and failure stages were predominant sepsis complications, in 27 (38%) and 26 (37%) subjects, respectively. In contrast, a previous study reported that AKI failure was more prevalent in pediatric patients with sepsis compared to AKI stage of injury.[26] These differences in outcomes may have been due to differences in patient characteristics and the primary diseases underlying the occurrence of sepsis.

Our 71 subjects had a median WBC count of 17.2 x 10^3/mm^3 with a wide range (1.1-80.2 x 10^3/mm^3). This WBC count cannot be used as a basis for the occurrence of AKI in sepsis patients, as expected WBC count values vary with age and sex.[27,28] Besides WBC, neutrophils, lymphocytes, and NLR were evaluated in the study. NLR value shows the subject's response to inflammation based on the

Table 4. Outcomes of AKI severity and PELOD-2 score

Variables	Survived (n=33)	Died (n=38)	OR (95%CI)	P value
AKI severity, n			3.04 (0.990 to 9.378)	0.052
Risk	12	6		
Injury and failure	21	32		
PELOD-2 score, n			47.6 (11.660 to 194.327)	< 0.001
<10	28	4		
≥10	5	34		

Table 5. Analysis of NLR and AKI severity

Variables	Mean NLR (SD)	r	P value
AKI severity		0.019	0.878
Risk	7.08 (4.50)	0.187	0.458
Injury	7.14 (4.51)	0.238	0.232
Failure	6.99 (4.29)	0.058	0.779

physiological relationship between neutrophils and lymphocytes, systemic inflammation, and stress. Sepsis induces a systemic cytokine-chemokine response that manifests as neutrophilia and lymphopenia due to severe immunological activation and dysfunction.[29] A higher NLR may indicate a severe inflammatory progression in the patient.[30] In our study, median NLR for pediatric patients with sepsis and AKI was 6.416, similar to a study which reported a median NLR of 6.03.[21]

Acute kidney injury is a sudden loss of renal function caused by decreased renal function.[31,32] In our study, the mean GFR decrease in each stage of AKI was obtained: AKI risk was 36.14%, AKI injury was 63.94%, and AKI failure was 86.64%. The AKI is caused by microcirculatory dysfunction, inflammation, bioenergy, and the adaptation of tubular cells to cellular stress. Inflammation has a role in the pathophysiology of AKI. Moreover, inflammatory markers, such as IL-6, IL-10, and procalcitonin have been associated with septic AKI, which plays a crucial role in systemic inflammation.[7] Association between NLR and the development of septic AKI is attributable to inflammation's function in the pathophysiology of AKI.[33] Our study found a positive correlation between NLR value and AKI severity.

We noted an increase in the mortality of pediatric patients with sepsis and AKI in the injury and failure stages by 3.04 times. A previous study reported an increase in mortality in sepsis patients with AKI by 5.6 times.[34] Sepsis and AKI are independent factors for increased mortality in patients with septic shock. Weiss et al. reported that of 1,685 subjects with sepsis, the incidence of renal impairment in the first three days was 9.6%.[35]

We also assessed the relationship of PELOD-2 scores with outcomes in pediatric patients with sepsis and AKI. Patients with a PELOD-2 score of ≥10 had increased mortality by 47.6 times. This result was in accordance with a study that noted increased risk of mortality in pediatric sepsis patients based on PELOD-2 scores, where PELOD-2 scores ≥11 having 8.3 times mortality risk,[25] while another study reported that a PELOD score of ≥10.5 increased the risk of developing AKI by 82.6%, and AKI patients had a mortality risk of up to 3.69 times.[36]

We found no significant correlation between NLR and AKI severity. Studies linking NLR values to AKI-accompanied sepsis patients in pediatric subjects have never been conducted, to the best of our knowledge. However, in adult subjects, an NLR of 6.7 could predict the occurrence of AKI in sepsis patients with a sensitivity of 90.7% and a specificity of 92.9%.[13]

Our study had some limitations. It was a retrospective study in a single center. In addition, we did not compare NLR with other markers of kidney injury. Also, diagnosis of AKI was based only on the increase in serum creatinine and GFR, while the role of urine output was not considered. We also did not compare the incidence of AKI with other risk factors that could have caused AKI in pediatric patients with sepsis.

In conclusion, AKI in sepsis may increase morbidity and mortality in children. We find no correlation of NLR value with AKI severity and there are no significant findings between these two variables, but the septic children with more severe AKI tend to be less survive. Further studies with a larger sample size are needed to elucidate the usefulness of NLR to predict AKI severity in children with sepsis.

Conflict of interest

None declared.

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