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Neutrophil Gelatinase-Associated Lipocalin Serum as a Predictor of Acute Kidney Injury in Pediatric Acute Lymphoblastic Leukemia with Induction Phase Chemotherapy

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KEYWORDS

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Abstract

AKI is more common in hematological cancers than in other forms of cancer caused by underlying malignancy or subsequent consequences of treatment. AKI affects 68.5% of people. AKI diagnostic criteria rely on creatinine and urine output, which cannot detect early kidney impairment. Neutrophil gelatinase-associated lipocalin has been studied as a marker for the early detection of AKI. This study aimed to evaluate serum NGAL as a predictor of AKI in pediatric ALL treated with induction-phase chemotherapy. This study was designed as an observational analysis in a prospective cohort from April to December 2022. 77 patients with induction chemotherapy met the inclusion and exclusion criteria at Dr. Moewardi Surakarta. A multivariate analysis with logistic regression was conducted to determine the relative risk and 95% confidence interval (CI) for each variable. The prevalence of AKI in this study was 40.3%. Haemoglobin, creatinine, and serum NGAL significantly differed (p = 0.381, 0.044, 0.000). The NGAL cut-off was 187.5 ng/mL, with a sensitivity of 80.6% and a specificity of 84.8%. Age, anemia, leukocytosis, and NGAL had an adjusted RR with CI of 95%, respectively 1.22 (95% CI 0.31-4.82; p=0.799), 2.07 (95% CI) 0.50-8.68; p=0.318), 7.45 (95% CI 1.26-44.09; p=0.027) and 33.10 (95% CI 7.64-143.40; p<0.001). In ALL children receiving induction-phase chemotherapy, serum NGAL levels of more than 187.5 ng/mL are an independent predictor of AKI. Follow-up research was conducted at different examination facilities to identify the diagnosis of AKI based on the completion of supporting exams and the timing of creatinine collection.

INTRODUCTION

In 2016, there were 60,140 new cases of leukemia diagnosed and 24,400 fatalities caused by all forms of leukemia, with Acute Lymphoblastic Leukemia (ALL) and acute myeloid leukemia (AML) contributing to about half of all new cases. The total age-adjusted incidence of leukemia, including acute and chronic variants, was 12.5 per 100,000 population, with Acute lymphoblastic leukemia (ALL) occurring at 1.6 per 100,000 and AML at 3.6 per 100,000 (O'Donnell, 2016). Acute lymphoblastic leukemia (ALL) is responsible for 75% of all childhood acute leukemias (Lanzkowskys et al., 2016). Acute Kidney Injury (AKI) is more common in patients with hematologic malignancies than in other forms of malignancy. Acute Kidney Injury (AKI) has a cumulative incidence range of 45.2% to 58.5% in patients with acute leukemia in 2 weeks and 77.2% to 88.4% in a year following diagnosis (Park et al., 2019). Acute Kidney Injury (AKI) significantly increased mortality in acute leukemia patients (62.5%) compared to those without AKI (37.5%) (Ballo et al., 2021).

Biomarkers for diagnosing early-onset AKI have been studied, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C, and liver fatty acid binding protein (L-FABP), showed great potential for early and accurate diagnosis (Soni et al., 2010). As an early biomarker, NGAL beat serum cystatin C; both L-FABP and NGAL were early predictors of AKI, but NGAL showed a greater area under the curve (AUC) with 100% sensitivity and

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specificity when compared to L-FABP (71% sensitivity and 68% specificity) (Soni et al., 2010). Li et al. (2019) conducted research to assess serum NGAL levels in identifying AKI caused by the administration of high-dose methotrexate therapy in children with Acute Lymphoblastic Leukemia (ALL). They reported that serum NGAL levels could be used to identify direct renal tubular damage induced by high-dose methotrexate therapy.

Much research has been conducted to identify Acute Kidney Injury (AKI) predictors utilizing NGAL biomarkers in various clinical settings. The number of AKI studies in young people is substantially lower than in the adult group, and the participants are often included in relatively small numbers (Bhojani et al., 2020). This study aimed to prove that serum NGAL may be used to predict Acute Kidney Injury (AKI) in pediatric acute lymphoblastic leukemia (ALL) patients receiving induction-phase chemotherapy.

MATERIALS AND METHOD

Participants

Observational research with a prospective cohort method was used to investigate serum NGAL as a predictor of AKI in children ALL treated with induction-phase chemotherapy. The research was done out at the Dr. Moewardi Regional General Hospital (RSDM) Clinical Pathology Installation in Surakarta. The study was conducted from October to December 2022, with sampling taken from April to December 2022. This study was approved by the biomedical research ethics committee at FK UNS/RSDM in Surakarta with number: 1.456/XI/HREC/2022 and patient consent.

All pediatric acute lymphoblastic leukemia (ALL) patients who had regular blood tests, peripheral blood testing (GDT), bone marrow puncture (BMP), and/or immunophenotyping were included in this research. According to Dahlan (2016)'s sample size calculation formula, the minimum sample size necessary in this investigation was 74 participants. In this study, the inclusion criteria were (i) patients diagnosed with acute lymphoblastic leukemia (ALL) who had received the first induction phase chemotherapy from the pediatric ward of RSDM; (ii) aged 0 to 18 years; and (iii) willing to participate in the study by filling out the research / informed permission form, while the exclusion criteria for this study included (i) patients with inflammation, from medical records seen the primary complaint, history of current disease, and results of supporting examinations, and (ii) have a history of renal malignancy, CKD, diabetes mellitus, cardiac dysfunction, cardiac surgery patients, pulmonary disease, administration of contrast media from medical records.

Treatment

The research method began with collecting the patient's primary data, obtaining a history of the patient's ailment, and completing an informed permission form. A single form was used to record and compile all exam results. The data were collected, statistical computations were performed, and the results table was created.

First, the performance test of the tool was carried out before examining the research sample. Analytical tests include precision/accuracy tests and accuracy/accuracy tests. One-day precision tests examined hemoglobin, leukocyte, creatinine and serum NGAL levels (Siregar et al., 2018). Precision is usually expressed in the value of the coefficient of variation (KV) in %, and the KV results of each parameter are hemoglobin 6.4%, leukocytes 15.1%, and creatinine 13.9%, which are lower than the maximum KV in the literature. Therefore, it can be concluded that the method carried out in this study was thorough (Siregar et al., 2018). The accuracy test results also follow the acceptable range, so it can be concluded that the accuracy of the examination in this study is good (Siregar et al., 2018).

Subjects had venous blood drawn in a closed system, as much as ± 3 cc of blood into a tube without anticoagulant to examine serum NGAL levels. The samples were centrifuged at 6,000 rpm for 10 minutes to separate the serum and then collected in aliquots. All sera were stored in a refrigerator at -80o C until analysis. The patient's hemoglobin and leukocyte levels were assessed based on medical record data.

NGAL examination is performed using ELISA. The ELISA microplate in this kit has been coated with a human NGAL-specific antibody. Samples or standards are added to the microplate well, and then human NGAL-specific antibody and avidin-horse radish peroxidase (HRP) conjugate are added to each well and incubated. Free components are removed by washing. Then the substrate solution is added to each well, producing a blue color. The enzyme-substrate reaction was stopped by adding a stop solution, and a yellow colour change

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occurred—the spectrophotometric method measured optical density (OD) at a wavelength of 450 nm. The OD value describes the concentration of human NGAL in the sample. With an analytical sensitivity of 0.1 ng/mL.

Statistical Analysis

The characteristics of the study variables were differentiated between the AKI and no AKI groups. The variables of age, sex, hemoglobin level, leukocyte level, creatinine level, and NGAL level are nominal scale categorical variables, reported as the number of subjects n (%). A comparison test was performed using the Chi-square test. Comparison tests between the AKI and no AKI groups used the unpaired t-test for normally distributed data and the Mann Whitney-U test for non-normally distributed data. The p-value was significant if <0.05. NGAL cut-off value (COV) for predicting AKI was obtained from the receiver operating characteristic (ROC) curve by calculating the AUC area under the curve (AUC) at various cut-off values, looking for the best cut-off at the intersection between sensitivity and specificity.

Bivariate analysis was performed to see the relationship between the independent variable, namely serum NGAL levels, with the incidence of AKI and also assessed the relationship between several variables that affect the incidence of AKI, namely age, gender, anemia and hyperleukocytosis. Analysis was performed using a 2x2 test table and d (%) = X - NA NA 48 looking for Relative Risk (RR) with a 95% confidence interval (CI). The p-value was significant when p<0.05. Multivariate analysis was performed on variables that had a significant effect on bivariate analysis (p<0.25) (Dahlan, 2016). Multivariate analysis was performed by analyzing the model with modification of the research variables. Furthermore, logistic regression analysis was performed so that the best predictor model was obtained to determine the probability of AKI in pediatric ALL with induction-phase chemotherapy. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 25.0.

RESULTS

The study subjects consisted of 42 (54.6%) males and 35 (45.4%) females, with the mean age of the subjects in this study being 7.71±4.72 years. ALL subjects with AKI were 31 subjects (40.3%), and those who did not experience AKI were 46 subjects (59.7%). The incidence of AKI based on stage AKI in the subjects of this study was found to experience stage 1 AKI as much as 100%. Data characteristics and variables of research subjects such as age, gender, hemoglobin, leukocytes, creatinine, and NGAL, each with a p-value = 0.381; 0.329; 0.044; 0.127; 0.003, and 0.001. The clinical characteristics that were significantly different between the two groups were hemoglobin, creatinine, and serum NGAL levels.

Table 1. Data characteristics and research subject variables

Indicator	AKI (n=31)	Non-AKI (n=46)	*p-value*
Age (years)[a]	8 (1-17)[κ]	6 (1-17)[κ]	0,381
Gender[c]			
Boys	19 (61,3%)	23 (50,0%)	0,329
Girls	12 (38,7%)	23 (50,0%)	
Hemoglobin (g/dL)[b]	9,21 ±2,37[#]	10,23 ±1,99[#]	0,044*
Leukosit (10^3/μL)[a]	8,9 (2,0-532,3)[κ]	6,6 (1,8-185,1)[κ]	0,127
Creatinine (mg/dL)[a]	0,2 (0,2-0,4)[κ]	0,2 (0,2-0,4)[κ]	0,003*
NGAL (ng/mL)[a]	249,0 (89,0-543,0)[κ]	127,5 (75,0-318,0)[κ]	0,001*

#: Normally distributed data (mean ± SD); κ: Non-normally distributed data, median (minimum-maximum); a: Mann Whitney test b: Independent t test; c: Chi square test (nominal data); *: significant at α=5% (0,05)

The performance of serum NGAL levels as a predictor of AKI in pediatric ALL with induction-phase chemotherapy is shown in the form of pictures and numbers in the ROC curve and area under the curve (AUC) (Figure 1). The AUC region was 0.855 with a 95%CI range of 0.755-0.955 (p<0.001).

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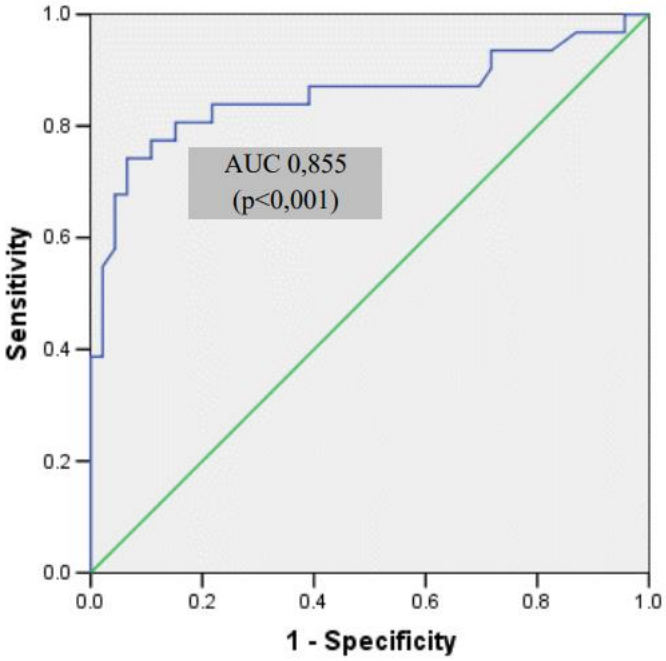

Figure 1. ROC curve and AUC area of serum NGAL as a predictor of incidence of AKI in pediatric ALL with induction phase chemotherapy

The sensitivity and specificity lines meet at the NGAL level of 187.5 ng/mL, which was chosen as the cut-off. The cut-off intersection's performance in terms of sensitivity and specificity is at its best, with 80.6% sensitivity and 84.8% specificity. The cut-off value of 187.5 ng/mL was divided into 32 participants (41.6%) with NGAL levels above or equal to the cut-off value, and 45 subjects (58.4%) below the cut-off value.

A 2x2 test table was used to analyze the association between variables that are risk factors for the occurrence of AKI in ALL children receiving induction-phase chemotherapy. The RR and a 95% confidence interval were found when the p-value was judged significant if it was 0.05. Based on Table 2, parameters that were significant in bivariate analysis with $p < 0.05$ were anemia, hyperleukocytosis and NGAL variables with RR 2.19 (95% CI 1.08-4.44; $p = 0.016$); RR 2.10 (95% CI 1.29-3.42; $p = 0.009$) and RR 5.86 (95% CI 2.72-12.62; $p < 0.001$), respectively. These parameters were continued to multivariate analysis to determine the strength of the association between these variables and the incidence of AKI.

Table 2. Results of bivariate analysis between independent variables and the incidence of AKI in pediatric ALL with induction phase chemotherapy

Variables	AKI		non-AKI		RR	95% CI	*p-value*
	n	%	n	%			
Age (yo)							
≤6	12	38.7	25	54.3	0.68	0.39-1.20	0.178
>6	19	61.3	21	45.7			
Gender							
Boys	19	61.3	23	50	1.32	0.75-2.33	0.329
Girls	12	38.7	23	50			
Anemia (g/dL)							
<10.5	24	77.44	23	50	2.19	1.08-4.44	0.016*
≥10.5	7	22.6	23	50			

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Variables	AKI		non-AKI		RR	95% CI	*p-value*
	n	%	n	%			
Hyperleukocytosis (/µL)							
>100.000	11	35.5	5	10.9	2.10	1.29-3.42	0.009*
≤ 100.00	20	64.5	41	89.1			
NGAL levels (ng/dL)							
≥ 187.5	25	80.6	7	15.2	5.86	2.72-12.62	<0.001*
< 187.5	6	19.4	39	84.8			

*Significant in p-value<0.05

Age, anemia, hyperleukocytosis, and NGAL levels with the incidence of AKI have been analyzed to multivariate analysis since the p-value was less than 0.25. (Table 3). The independent variables included in the multivariate analysis, namely age, anemia, leukocytosis and NGAL level >187.5 ng/mL, had adjusted RR with 95%CI of 1.22 (95%CI 0.31-4.82; p=0.799); 2.07 (95%CI 0.50-8.68, p=0.318); 7.45 (95%CI 1.26-44.09; p=0.027) and 33.10 (95%CI 7.64-143.40; p=0.05). Age and anemia did not influence the incidence of AKI in ALL children with induction-phase chemotherapy (p>0.05). While hyperleukocytosis and NGAL show that they influenced the incidence of AKI in ALL children with induction-phase chemotherapy, serum NGAL levels were the most dominant and significant influence (p<0,05). It can be concluded that serum NGAL can predict the incidence of AKI in ALL children with induction-phase chemotherapy.

Table 3. Results of multivariate logistic regression analysis between independent variables with the incidence of AKI in pediatric ALL with induction phase chemotherapy

Variables	Adjusted RR (95%CI)	*p-value*
Age	1.22 (0.31-4.82)	0.799
Anemia	2.07 (0.50-8.68)	0.318
Hyperleukocytosis	7.45 (1.26-44.09)	0.027*
NGAL (≥187.5 ng/mL)	33.10 (7.64-143.40)	<0.001*

*Significant in p-value<0.05

DISCUSSION

This study found that the age of AKI patients had a median of 8 years, while those without AKI had a median of 6 years. Gender in AKI and non-AKI patients had the same proportion of men and women, with test results showing no significant difference in the proportion of patients based on age or gender. The bivariate analysis also found that age and gender had no significant association with AKI in pediatric ALL with induction-phase chemotherapy. In two studies, age is one of the risk variables for AKI. Nimkar et al. (2020) and Hirsch et al. (2020) both reported odds ratio (OR) values of 1.03 (p 0.001) and 1.03 (p 0.007), respectively. This results study was also different from research conducted by Bhojani et al. (2020) and Nisula et al. (2014), which found that AKI was diagnosed more often in children less than or equal to six years and girls associated with lower total body water. The difference between this study and the study by Bhojani et al. (2020) may be caused by several factors, including the fact that this study had fewer patients (n = 77) than the study by Bhojani et al. (n = 1,112), had an average age range of seven to eight years, and did not meet the requirements for incidence per variable. The study by Bhojani et al. mentioned the incidence of AKI more frequently at less than or equal to six years.

According to earlier studies, women are expected to have fewer glomeruli than males. Reduced renal functional reserve, decreased glomerular filtration rate, and increased sensitivity to hyperfiltration are the results of fewer nephrons (Luyck et al., 2011). This study differs from previous studies due to the more significant number of male subjects (54.6%) compared to the number of female subjects (45.4%). Anemia is one of the risk factors for AKI, according to research by Han et al. (2015). Since the kidneys have the highest oxygen requirements in the body and normally receive 20–25

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percent of blood from the cardiac output, anemia frequently results in ischemic conditions because it reduces the amount of oxygen in the blood Han et al. (2015).

Anemia was a factor in this study, and it resulted in an adjusted RR value of 2.07 (95%CI 0.50-8.68) and a p-value of 0.318 (p>0.05), indicating that it wasn't the main factor determining the incidence of AKI in children with pediatric ALL receiving induction phase chemotherapy. In accordance with Gameiro and Lopes (2019), several studies have shown the link between anemia, which frequently develops in hospitalized patients and is linked to worse outcomes in the prevalence of AKI..

The impact of anemia on the development of AKI is probably complicated. Patients are more vulnerable to renal hypoxia and oxidative stress when their hemoglobin levels are lower (Gameiro & Lopes, 2019). Anemia did not increase the risk of progression to stage III AKI, or it can be inferred that anemia is not associated with an increased risk of progression to more severe AKI, according to a retrospective study by Powell-Tuck et al. (2016) of 210 patients with stage I AKI diagnosed using AKIN classification criteria. Several studies have shown that anemia can cause AKI, but this study did not illustrate that anemia affects the incidence of AKI in ALL children with induction-phase chemotherapy. This may be due to taking the reference value of hemoglobin levels too high (<10.5 mg/dL) or differences with the study population.

In this study, hyperleukocytosis had a 2.10 times greater risk of AKI than patients without hyperleukocytosis (leukocytes <100,000/µL). The results of the multivariate analysis also showed that the adjusted RR value = 7.45 (95%CI: 1.26-44.09). The results of this study are in inline with Abla et al. (2016), who state that hyperleukocytosis can cause early complications in the form of renal dysfunction, which occurs in as much as 6% of ALL patients (Abla et al., 2016). Research by Bhatia et al. (2013) found that structural and functional kidney changes in acute leukemia are caused by hyperleukocytosis, therapy-related side effects, and infiltration. Abla et al. (2016) studied the incidence of hyperleukocytosis in acute leukemia, which ranges from 5-13% in AML to 10-30% in ALL.

While there are no clear diagnostic criteria for hyperleukocytosis, it can be described as an abnormality in routine blood laboratory tests when the white blood cell count is more significant than 100,000/L (Korkmaz, 2018). Leukostasis, tumor lysis syndrome (TLS), and disseminated intravascular coagulation (DIC) are three laboratory abnormalities that might increase mortality (Gong et al., 2014). Hyperleukocytosis with symptoms is referred to as leukostasis, and it can cause cerebral bleeding, renal failure, and respiratory failure. Prior to this investigation, the pathophysiology of leukostasis was unknown.

This study found that serum NGAL levels have a significant relationship with AKI in pediatric ALL children with induction-phase chemotherapy. The AUC value was 0.855, meaning 85.5% of the incidence of AKI can be predicted by serum NGAL. The cut-off value of serum NGAL as a predictor of the incidence of AKI in ALL children with induction phase chemotherapy is 187, 5 ng/mL with a sensitivity of 0.806 and a specificity of 0.848. Research by Chae et al. (2015) showed that NGAL levels in 199 patients with MM varied between 15 and 1,300 ng/mL, with a median value of 92 ng/mL. The cut-off obtained was 184 ng/mL with a sensitivity of 88.9% and specificity of 85.3% (AUC 0.907).

Li et al. (2019) conducted a study on serum NGAL as a biomarker to predict acute kidney injury in pediatric ALL with high-dose methotrexate administration. The results of the study showed that serum NGAL cut-off 24 hours after methotrexate administration had a value of 295 ng/mL with 68% sensitivity and 90% specificity Li et al. (2019). NGAL formation occurs in epithelial cells, which maintain renal tubular structure and organ homeostasis and function. When renal tubular cells are damaged, an automatic cellular response occurs to increase NGAL levels in the body (Cassidy et al., 2019). The results of this study have a cut-off of 187.5 ng/mL, following the research of Makris et al. (2015), which states that NGAL regulation in healthy kidneys is formed by various cell types with low levels. NGAL levels in the serum of healthy adults range from 28.7 ng/mL to 167.0 ng/mL.

NGAL levels increase proportionally with the severity and duration of kidney injury, expressed within 1-3 hours of kidney damage and 36-72 hours before the increase in creatinine (Rizvi & Kashani, 2017). Corbacioglu et al. (2017) reported that NGAL levels increase from the first 2 hours of AKI and reach a peak after 6 hours and persist for five days until then decreasing. Recent data suggest that the NGAL test is also able to detect patients with only subclinical or moderate kidney damage, which may

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not be revealed by significant variations in renal function tests (Clerico et al., 2012).

Limitations. Since the study was only done at one health centre, it only reflects the people who were there when the researcher was there. This study used creatinine levels rather than urine production to diagnose AKI solely based on the KDIGO criteria. Additionally, this study did not allow us to determine the creatinine sampling time simultaneously.

CONCLUSION

Acute Kidney Injury (AKI) in acute lymphoblastic leukemia (ALL) pediatric receiving induction-phase chemotherapy is independently predicted by serum NGAL levels ≥187.5 ng/mL. Follow-up studies were conducted at several examination facilities, and the diagnosis of AKI was made using the results of supporting tests and the timing of creatinine collection at the same time.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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