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Original Article

Risk factors of acute kidney injury in pediatric acute lymphoblastic leukemia with hyperleukocytosis

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Abstract

Background Acute kidney injury (AKI) can be found in pediatric acute lymphoblastic leukemia (ALL) patients with hyperleukocytosis. Acute kidney Injury (AKI) increases hospital length of stay and mortality. Previous studies have only reported the AKI incidence in ALL patients with hyperleukocytosis, without clarifying risk factors attributed to AKI incidence.

Objective To determine the risk factors of AKI in pediatric ALL patients with hyperleukocytosis.

Methods A case-control study was conducted in children aged 1-18 years admitted to Dr. Sardjito Hospital (RSUP Dr. Sardjito), Yogyakarta, Central Java. Total population sampling of pediatric ALL patients with hyperleukocytosis and AKI was used for the case group, and a simple random sampling ratio of 1:2 was used for the control group. Cut-off values for each independent variable were determined by receiver-operator characteristic (ROC) curves. Bivariate and multivariate analyses were performed on potential risk factors.

Results Fourteen pediatric ALL patients with hyperleukocytosis and AKI were included in the case group and 28 children with ALL and hyperleukocytosis but without AKI were included in the control group. The incidence of AKI in children with ALL and hyperleukocytosis was 15.4%. Multivariate analysis revealed that the significant risk factors of AKI in ALL patients with hyperleukocytosis were phosphate concentration ≥5.15 mg/L (OR 10.43; 95%CI 1.38 to 79.04; P=0.02) and uric acid concentration ≥9.08 mg/dL (OR 12.39; 95%CI 1.88 to 81.44; P=0.009).

Conclusion Phosphate concentration ≥5.15 mg/L and uric acid ≥9.08 mg/dL are risk factors of AKI in pediatric ALL patients with hyperleukocytosis. **[Paediatr Indones. 2023;63:433-42; DOI: https://doi.org/10.14238/pi63.6.2023.433-42**].

Keywords: *risk factor; acute kidney injury; acute lymphoblastic leukemia; children; hyperleukocytosis*

Acute kidney injury (AKI) is associated with high mortality rate in children. The mortality rate of children with AKI admitted to intensive care at RSUP Dr. Sardjito, Yogyakarta, Central Java, in 2010-2016 was 78.2%.[1] AKI is one of several manifestations found in pediatric malignancies, with an incidence rate of 16.9%.[2] Pediatric patients with malignancy-associated AKI who required renal replacement therapy (RRT) had a high mortality rate of 73%.[3]

Acute lymphoblastic leukemia (ALL) is a common pediatric hematologic malignancy. The annual incidence rate in the United States was 3.7-4.9 cases in 100,000 children aged 0-14 years, with a peak incidence at 2-5 years of age.[4] The incidence rate of ALL in Yogyakarta in 1998-2009 was 496 cases, which comprised 74.5% of acute leukemia cases overall in Yogyakarta.[5] Hyperleukocytosis features in 18.3% of ALL cases.[6] Hyperleukocytosis

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is defined as increased peripheral blood leukocytes of >50,000/μL.[7] Hyperleukocytosis is caused by excessive proliferation of blast cells.[8] High numbers of blast cells in the bloodstream can induce intravascular aggregation leading to the obstruction of peritubular and glomerular capillaries, subsequently evolving into AKI.[9] Hyperleukocytosis is also a risk factor for tumor lysis syndrome (TLS). Rapid turnover or breakdown of tumor cells in TLS causes metabolic dysfunction and induces AKI.[10] The incidence of AKI in pediatric ALL with hyperleukocytosis was not high at 9%, however, AKI increases hospital length of stay and mortality of children with malignancies.[3,11] AKI in children with malignancy, in particular ALL with hyperleukocytosis, can affect outcomes of therapeutic management. If AKI occurs during malignancy therapy, dosage adjustment or even discontinuation of several chemotherapeutic agents such as methotrexate may be required.[3]

Several factors have been associated with the incidence of AKI in patients with malignancies in general. Younger age was considered to be a risk factor for AKI in children. An Indian study reported that age 1-5 years was a risk factor for AKI (OR 2.3; 95%CI 1.24 to 4.8).[12] Younger children may have less mature renal function than older ones.[13] Low hemoglobin level was also significantly correlated with AKI. A retrospective study in China reported low hemoglobin as a risk factor of AKI in patients with malignancy (OR 1.78; 95%CI 1.64 to 1.92).[14] Low hemoglobin level might directly reduce oxygen delivery to the kidneys, inducing tissue hypoxia and progressing into AKI.[15]

The ALL patients with TLS could experience metabolic disorders including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Uric acid is associated with renal dysfunction, as higher levels increase the risk of AKI. High uric acid may lead to sedimentation in renal tubules, renal vasoconstriction, autoregulation dysfunction, reduced renal blood flow, and inflammation.[10] Hyperuricemia was found to increase the risk of AKI by 4.32-fold in children with hematologic malignancies (OR 4.32; 95%CI 1.60 to 11.67).[16] The increment of calcium phosphate solubility to more than 60 mg/dL increases precipitation risk in microvascularization and renal tubules.[10] A study in adult patients at Seoul National University Bundang Hospital showed that a patient group with phosphate concentration > 3.8 mg/dL had 2.8 times the risk of developing AKI (OR 2.8; 95%CI 2.44 to 3.22).[17]

A retrospective cohort study in adults with malignancy reported that hyperleukocytosis patients had a greater risk of developing AKI (OR 1.76l; 95%CI 1.57 to 1.98).[14] ALL patients with leukocyte count > 100,000 /μL are considered a high risk group who are prone to TLS, in turn 14% TLS have AKI.[18,19] Hyperhydration is one of the supportive therapies for hyperleukocytosis patients. The aim of hyperhydration is to reduce blood viscosity due to increasing leukocyte count, thus preventing leukostasis and renal excretion of metabolites would be increased, including potassium, uric acid, and phosphate.[20]

Previous studies have reported only the incidence of AKI in ALL pediatric patients with hyperleukocytosis without clarifying risk factors attributed to AKI.[11,21,22] Elucidation of AKI risk factors in children with ALL and hyperleukocytosis are needed for clinicians to detect and perform early interventions to prevent progression to AKI.[3]

Methods

This analytical, observational study with case control design was performed in children aged 1-18 years who were admitted to RSUP Dr. Sardjito, Yogyakarta, Central Java, with a diagnosis of ALL and hyperleukocytosis between January 2017 and December 2021. We retrospectively traced possible risk factors for AKI in ALL patients with hyperleukocytosis.

The inclusion criteria for the case group were children aged 1-18 years, admitted for ALL with hyperleukocytosis, and had at least two serum creatinine examination results during their hyperleukocytosis stage ≥ 0.3 mg/dL in 48 hours, or 1.5 times higher compared to the predicted baseline value during the previous 7 days. The exclusion criteria for the case group were incomplete medical record data, an initial serum creatinine of > 1.5 times higher than baseline value taken from the lowest serum creatinine level during hyperleukocytosis, or had a history of chronic kidney disease. The inclusion criteria for the control group were children aged 1-18 years with ALL and hyperleukocytosis admitted with

at least two serum creatinine examination results during hospital stay, yet not fulfilling the inclusion criteria for the case group. The exclusion criteria for the control group were incomplete medical record data or a history of chronic kidney disease. Case subjects were recruited by total sampling method, while control subjects were chosen by a computer-based simple random sampling method.

The dependent variable was the incidence of AKI in children with ALL and hyperleukocytosis. Independent variables were age, leukocyte count, hemoglobin level, phosphate level, uric acid level, and hyperhydration therapy as possible risk factors for AKI.

Statistical analysis was performed using the *Statistical Package for Social Science (SPSS) version 25*. Univariate analysis was performed to assess the characteristics and distribution of data. Categorical variables were depicted as frequency and percentage. Numerical variables were described as mean and standard deviation (SD) if the data were normally distributed, or as median and range if the data were not normally distributed. Data transformation from numerical to categorical was performed based on optimal cut-off points by ROC curve variables of leukocyte count, hemoglobin, phosphate, and uric acid levels shown in apendices. Bivariate analysis was performed with Chi-square/Fisher's exact tests for categorical data, with statistical significance level of $P<0.05$. Normality test was performed with Kolmogorov-Smirnov test. Variables with P values <0.25 on bivariate analysis were further examined by multivariate analysis using logistic regression. OR and 95% CI were utilized to describe relationships between variables, with statistical significance level of $P<0.05$. This study was approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Universitas Gadjah Mada/RSUP Dr. Sardjito.

Results

This study was conducted using secondary data of children with ALL and hyperleukocytosis who were admitted to RSUP Dr. Sardjito between January 2017 and December 2021. A total of 144 children with hyperleukocytosis were noted in that period using ICD-10 codes (other specified disorder of white blood cells D72.82 and ALL C91.00) from the medical records. Eight patients had a single serum creatinine measurement, thus, these patients did not fulfill the inclusion criteria. A total of 136 patients met the inclusion criteria, 21 with AKI and 115 without AKI. Six patients were excluded due to incomplete medical records and/or had an initial creatinine >1.5 baseline creatinine during hyperleukocytosis in the case group and 45 patients were excluded due to incomplete data in the control group. Thus, 14 subjects fulfilled the inclusion criteria of the case group (total sampling method). The control group was chosen by simple random sampling at a ratio of 1:2, thus, with a total of 28 subjects included (**Figure 1**).

Subjects' characteristics are shown in **Table 1**. The mean age of subjects was 7.17 (SD 4.80) years in the case group and 8.27 (SD 4.40) years in the control group. Independent variables were categorized based on cut-off values from the ROC curve analysis, as shown in **Appendix 1**. The cut-off values were 5.5 years for age, 96,975/μL for leukocyte count, 6.45 g/dL for hemoglobin level, 5.15 mg/L for phosphate level, and 9.08 mg/dL for uric acid level (**Appendix 2**). Chi-square/Fisher's exact tests were utilized for bivariate analysis of categorical data. The variables with P values <0.25 were included in multivariate analysis: age, hemoglobin level, phosphate level, and uric acid level. Bivariate analysis results are shown in **Table 2**, along with multivariate analysis results.

Bivariate analysis showed that phosphate levels $\geq$ 5.15 mg/dL and uric acid levels $\geq$ 9.08 mg/dL were associated with the incidence of AKI. Variables with a P value > 0.25 in the bivariate analysis were included in the multivariate analysis include the variables age, hemoglobin phosphate levels and uric acid levels. Multivariate analysis showed the significant risk factors of AKI in pediatric ALL patients with hyperleukocytosis were phosphate concentration $\geq$5.15 mg/L and uric acid concentration $\geq$9.08 mg/dL.

Phosphate concentration $\geq$5.15 mg/L and uric acid $\geq$9.08 mg/dL were risk factors of AKI in pediatric ALL patients with hyperleukocytosis.

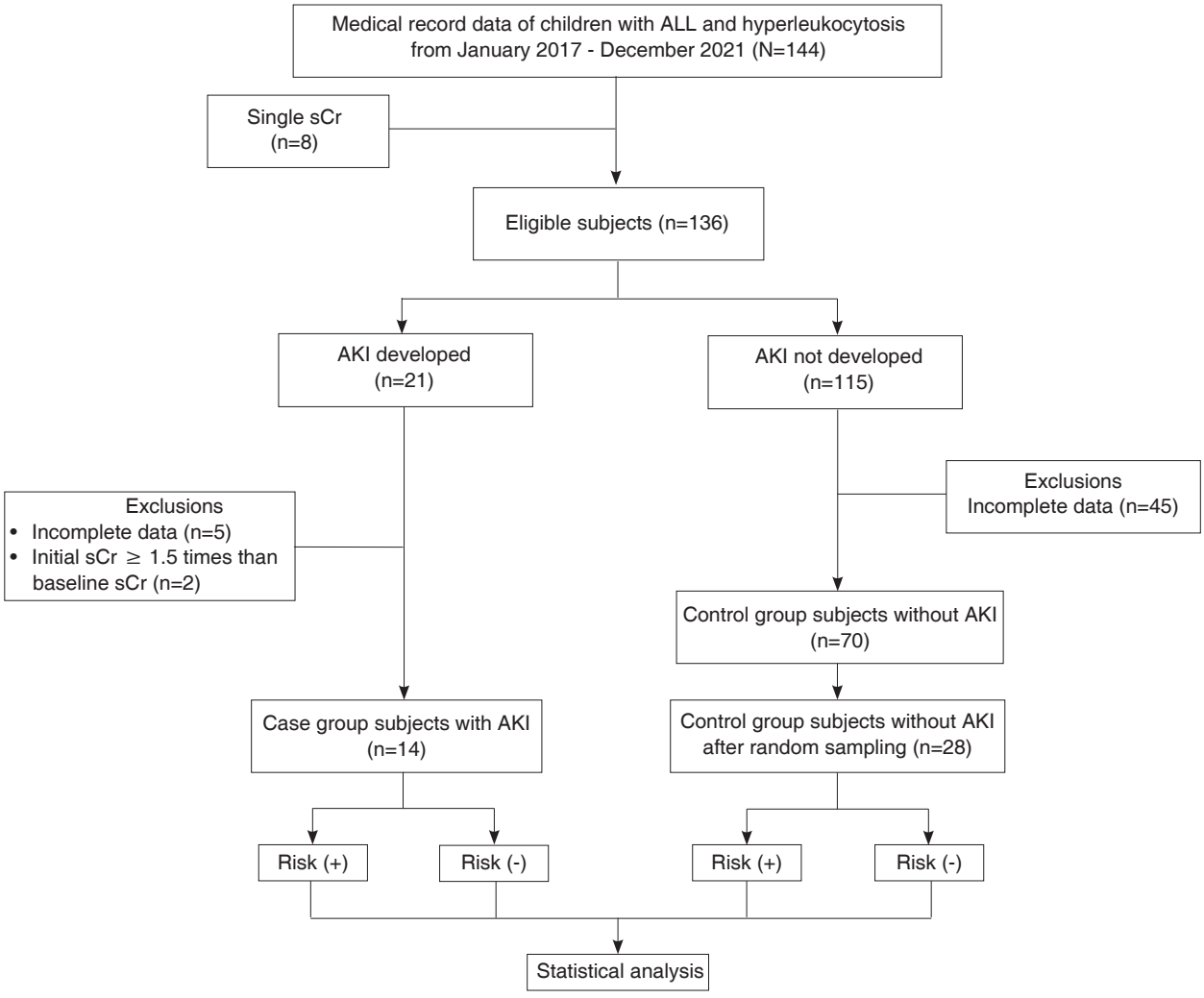

Figure 1. Subject recruitment flow chart

Discussion

The incidence of AKI in children with ALL and hyperleukocytosis in RSUP Dr. Sardjito, Yogyakarta, Central Java, between January 2017 and December 2021 was 15.4%. This result was higher compared to that of previous studies, which were 4.3%, 6%, and 9%.[11,21,22] In contrast, a study revealed an incidence of 20.83%.[23] The difference in study results could have been due to different renal failure criteria among studies.[21,22]

Male patients in our study were less likely to develop AKI, yet male sex was not a significant risk factor for AKI incidence. In contrast, more males were reported developed AKI, with a proportion of 62.2% of all critical children and a 1.742 times higher risk of AKI, although the pathophysiology was not clearly defined.[24] ALL was more common in males than females.[25] In our study the number of male and female who experienced AKI was same.

Hospital length of stay was significantly longer for subjects with AKI. Similarly, a study in China reported longer length of stay in patients with AKI than in those without AKI (33 days *vs.* 28 days, respectively; $P<0.001$).[2] A longer length of stay was likely due to ALL patients with AKI requiring a chemotherapy dosing adjustment based on their renal function, thus, affecting the outcome of therapy and prolonging the hospital stay.[3]

Table 1. Subjects' characteristics

Characteristics	AKI (n=14)	AKI not developed (n=28)
Gender, n		
Male	7	17
Female	7	11
Mean age (SD), years	7.17 (4.80)	8.42 (4.64)
Mean length of stay (SD), days	13 (5)	10 (3)
AKI staging, n		
Stage 1	4	
Stage 2	6	
Stage 3	4	
Early hyperhydration, n		
No	6	9
Yes	8	19
BMP results, n		
L1	5	13
L2	5	10
L1-L2	3	4
No data	1	1
Immunophenotyping, n		
B cells	1	
T cells	4	
No data	9	
TLS risk, n		
High	9	16
Intermediate	5	12
Median leukocyte count (range), /µL	119,625 (57,740-666,420)	111,790 (53,130-387,400)
Mean hemoglobin level (SD), g/dL	7.87 (2.58)	8.69 (2.94)
Mean phosphate level (SD), mg/dL	4.91 (3.14)	4.11 (0.96)
Mean uric acid level (SD), mg/dL	10.85 (6.01)	6.78 (2.34)

Hyperhydration is prefered method to prevent AKI.[26] Hyperhidration is useful to maintain renal blood flow, as well as increase the excretion of potassium, uric acid, and phosphate.[26,27] However, this theory was not in agreement with our study findings. In our study, not having hyperhydration was not a risk factor for AKI. Similarly, a previous study on children with TLS noted no significant difference in the initial volume of fluid administration for TLS children without AKI or with mild AKI compared to the volume of fluid administered to those with severe AKI (P=0.94).[28] In our study, those who did not receive hyperhydration developed AKI more often than those who did not, yet the result was not statistically significant. The reason could have been due to our utilizing secondary data. Furthermore, for those who received hyperhydration, correct administration was not clearly defined nor were the records clear as to if monitoring was adequately performed. Hyperhydration without good fluid balance monitoring might lead to fluid overload, which is one of the risk factors of AKI development.[29]

In our study, patients with ALL and hyperleukocytosis aged ≤5.5 years had 3.76 times higher risk of developing AKI, yet this result was not statistically significant. Similarly, a previous study reported no significant difference in age between children with and without AKI.[3] However, another study found that critically ill children aged 1-5 years had a higher risk of developing AKI. The different results between studies could have been due to different populations included in the study.[12] The high fractional volume of leukocytes in hyperleukocytosis can increase blood viscocity. Blast cells, which tend to maintain their shape, can obstruct small vessels and reduce blood flow in large caliber vessels. Blast cell aggregation in the microcirculation might

Table 2. Bivariate and multivariate analyses

Independent variables	AKI incidence		Bivariate analysis		Multivariate analysis	
	AKI (n=14)	AKI not developed (n=28)	OR (95%CI)	P value	OR (95% CI)	P value
Age, n						
≤5.5 years	7	7	3.00 (0.77 to 11.60)	0.165^	3.76 (0.57 to 24.77)	0.169
>5.5 years	7	21				
Gender						
Male	7	17	0.65 (0.18 to 2.36)	0.508x		
Female	7					
Early hyperhydration						
No	6	9	1.58 (0.42 to 5.94)	0.495x		
Yes	8	19				
Leukocyte count						
≥96,975 /µL	10	15	2.17 (0.55 to 8.59)	0.266x		
<96,975/µL	4	13				
Hemoglobin level						
≤6.45 g/dL	6	5	3.45 (0.82 to 14.47)	0.136^	6.26 (0.92 to 42.42)	0.060
>6.45, g/dL	8	23				
Phosphate level						
≥5.15, mg/dL	6	3	6.25 (1.26 to 30/90)	0.040*^	10.43 (1.38 to 79.04)	0.023*
<5.15,mg/dL	8	25				
Uric acid level						
≥9.08,mg/dL	8	5	6.13 (1.46 to 25.73)	0.015*^	12.39 (1.88 to 81.44)	0.009*
<9.08,mg/dL	6	23				

*significant P<0.05; xChi-square; ^Fisher exact test

induce organ dysfunction, including in kidneys. The aggregation of blast cells can obstruct the glomerular and peritubular capillaries, leading to reduced GFR.[7,9] In our study, patients with leukocyte count ≥96,975/µL had 2.17 times higher risk of AKI but the difference was not statistically significant. A previous study also noted no significant difference in the incidence of AKI in children with ALL between those with leukocyte count 100,000-200,000/µL and >200,000 /µL (17.3% *vs.* 27.7%, respectively; 95%CI 0.247 to 1.204; P=0.546).[30] According to a previous study, leukostasis in ALL patients occurred in those with higher leukocyte level compared to AML patients. This might have been due to the larger size and stiffness of myeloblasts, inducing leukostasis. Lymphoblasts have a smaller size, thus leukostasis in ALL is more likely in patients with higher leukocyte count. Leukocytosis in ALL might occur if the leukocyte count >400,000/µL.[11] The lack of a significant result could have been due to hyperhydration intervention either at first admission to the referral hospital or at the time of admission to RSUP Dr. Sardjito, leading to increased intravascular fluid and reduced blood viscocity, thus reducing the risk of AKI. Although the risk of AKI due to the aggregation of blast cells still might happen.

Subjects with hemoglobin level ≤6.45 gram/dL had a 6.26 times higher risk of AKI, although the result was not statistically significant. In contrast, a study stated that low hemoglobin level was a significant risk factor for AKI in malignancy patients (OR 1.78; 95%CI 1.64 to 1.92).[14] Anemia directly reduces oxygen concentration to the kidney, leading to tissue hypoxia and developing into AKI.[31] Hypoxia due to anemia damages renal tubuluar cells which are sensitive to oxygen level changes.[15] The lack of significance could have been due to our small sample size and/or differences in cut-off values used.

Phosphate level ≥5.15 mg/dL significantly increased the risk of AKI by 10.43-fold. This finding was in agreement with a study on TLS outcomes in children with hematological malignancy; patients with hyperphosphatemia developed AKI (OR 6.36; 95%CI 2.78 to 14.58; P<0.001). Hyperphosphatemia increases the formation of calcium phosphate crystals, increasing the risk of AKI.[16] This finding could be

of substantial help to clinicians who are considering aggressive hyperphosphatemia therapy to reduce phosphate levels in pediatric ALL patients with hyperleukocytosis, either using aggressive fluid therapy or with phosphate binders.

Uric acid level ≥9.08 mg/dL was also a significant risk factor, increasing the risk of AKI by 12.39 times. According to a previous study on children with TLS, hyperuricemia increased the risk of AKI by 4.32 times (OR 4.32; 95%CI 1.60 to 11.67). AKI may occur in hyperuricemic conditions due to uric acid stone formation.[16] Uric acid has negative effects on the kidney as it induces renal vasoconstriction and increases renal oxidation as well as inflammation.[32] Endothelial dysfunction might occur due to hyperuricemia through the inhibition process of nitric oxide (NO), further damaging the kidneys.[33] Acidic urine increases the risk of uric acid precipitation in the renal tubules. Urine acidity was not examined in our study due to limited data. However, clinicians ought to be aware that acidic urine can induce uric acid precipitation even at uric acid levels not exceeding 9.08 mg/dL. This significant result is important for clinicians to consider starting aggressive therapy to combat hyperuricemia.

Previously conducted studies on AKI in pediatric ALL patients with hyperleukocytosis reported only the incidence of AKI. We analyzed possible risk factors of AKI in such patients. We hope our findings will help clinicians in therapeutic management and prevention of AKI in patients with hyperleukocytosis. There were several limitations in our case control study. We utilized secondary medical record data which is prone to information bias. The determination of hyperhydration was also questionable, and the initiation time of hyperhydration and quality of fluid monitoring were not clearly defined. The laboratory examinations of leukocyte count, hemoglobin, uric acid, and phosphate levels in our study were not performed at the same patient presentation time nor with the same laboratory equipment, thus, variability in specimens and instruments might have affected the measurements. Furthermore, the small sample size and focus on one hospital means that our cut-off parameters cannot be generalized to all populations of pediatric ALL patients with hyperleukocytosis.

In conclusion, phosphate level > 5.15 mg/L and uric acid level > 9.08 mg/dL are significant risk factors for AKI in pediatric ALL patients with hyperleukocytosis, while age, leukocyte count, hemoglobin level, and no hyperhydration were not significant risk factors. Further studies on risk factors of AKI involving more than one health center should be conducted so that results can be applied more generally.

Conflict of interest

None declared.

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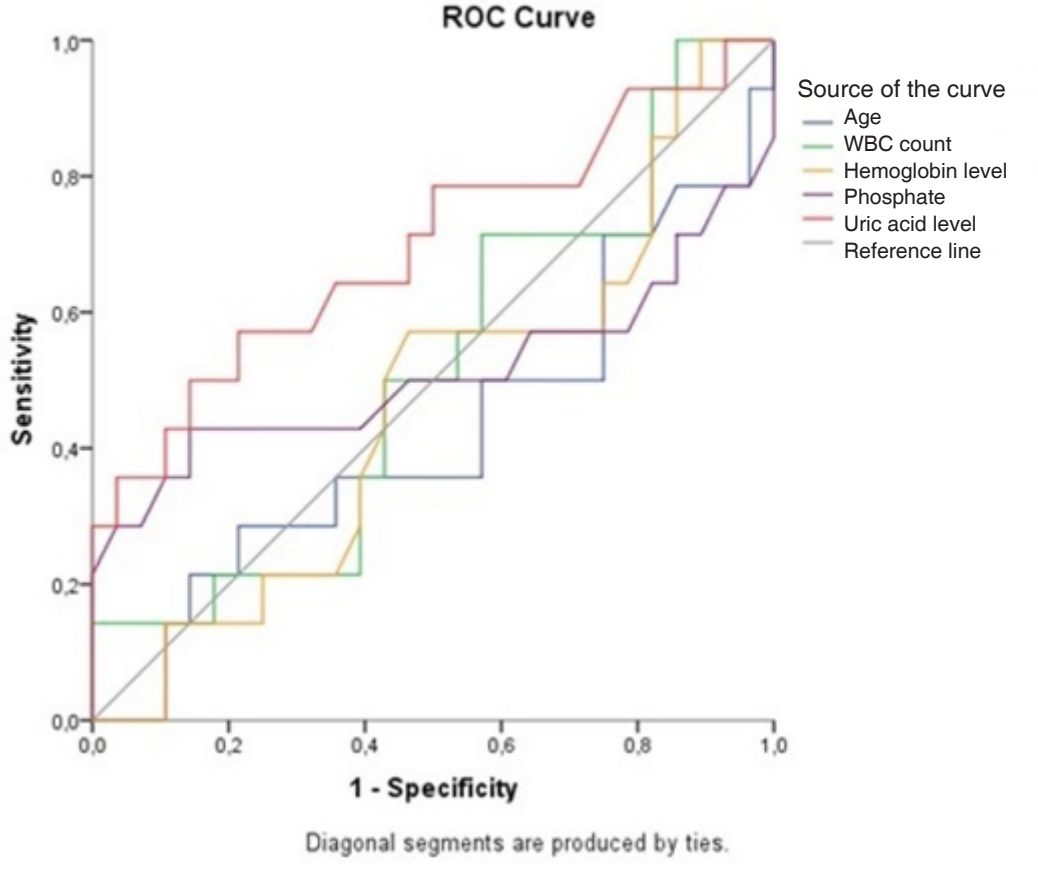
Appendices



Appendix 1. ROC curve for age, WBC count, hemoglobin, phosphate, and uric acid levels

Appendix 2. Table of cut-off values for each independent numerical variables

Independent variables	AUC	95%CI	Cut-off Youden Index	Sensitivity	Specificity	P value
Age	0.41	0.22 to 0.60	5.53	50.0	25.0	0.344
WBC count	0.56	0.38 to 0.74	96,975	71.4	46.4	0.522
Hemoglobin level	0.43	0.44 to 0.62	6.45	57.1	17.9	0.439
Phosphate level	0.52	0.29 to 0.75	5.15	42.9	89.3	0.841
Uric acid level	0.71	0.52 to 0.89	9.08	57.1	82.1	0.030