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ORIGINAL ARTICLE

Risk factors of tumor lysis syndrome in childhood acute lymphoblastic leukemia

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ABSTRACT

BACKGROUND
Acute lymphoblastic leukemia (ALL) is the most common childhood hematologic malignancy. Treatment failure in ALL can be caused by severe and life-threatening complications, including tumor lysis syndrome (TLS). Delay in identifying risk factors and establishing the diagnosis of TLS by clinicians can be fatal. This study aimed to determine the risk factors for TLS in children with ALL.

METHODS
This was a retrospective cross-sectional study on 81 children aged 0 to 18 years with ALL. Tumor lysis syndrome comes in two forms: laboratory and clinical. Laboratory TLS occurs if uric acid levels >normal values, potassium >6mEq/L, phosphate >6.5mg/dl, and calcium <7mg/dl. Clinical TLS includes an increase in serum creatinine, the presence of heart attacks, sudden death, and seizures. Risk factors for TLS include age, nutritional status, leukocyte count, presence of organ infiltration, presence of mediastinal mass, uric acid level, renal function, and type of chemotherapy regimen. Risk factors were analyzed using simple and multiple logistic regression analyses. A value of $p<0.05$ indicates a significant risk factor.

RESULTS
Twenty seven patients (33.3%) experienced TLS. Adjusted OR analysis showed that the presence of organ infiltration (aOR 5.42; 95% CI 1.45-20.27; p=0.012), leukocyte count (aOR 8.70; 95% CI 1.67-45.13; p=0.010), and decreased kidney function (aOR 12.21; 95% CI 1.09-136.89; p=0.042) were significant risk factors for TLS.

CONCLUSION
Decreased renal function, leukocyte count, and organ infiltration were significant risk factors for TLS. We suggest more vigilant assessment and monitoring to recognize and treat those patients who are at risk of TLS.

Keywords : Acute lymphoblastic leukemia, tumor lysis syndrome, risk factor, renal function, children

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common hematologic malignant disease in children. The prevalence of ALL reaches 75-80% of all cases of hematologic malignancies in children. Currently, with the advancement of medical science, ALL patients have a good prognosis. However, the mortality and morbidity rates of ALL patients in Indonesia are still higher than those of developed countries.[1] The appearance of severe and life-threatening complications causes therapeutic failure in patients with ALL. Due to its chemosensitive nature, the most common complication in pediatric patients with ALL is tumor lysis syndrome (TLS), which is a series of metabolic abnormalities that include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, with or without clinical results of toxicity due to these metabolic abnormalities.[2,3] Budiarto [1] found that 31.7% of ALL patients experienced TLS at Dr. Soetomo Hospital.

Tumor lysis syndrome is a common fatal complication in ALL patients. The mortality rate associated with TLS in children with hematologic malignancies was 21.4%.[4] Delay by clinicians in recognizing risk factors and diagnosing TLS can be fatal. Patients at risk for TLS must be identified because it is a preventable disorder that can develop quickly.[5] It can cause multiple organ compromise and ultimately death if left untreated. Effective management of TLS requires early identification of risk factors for development in addition to close observation and medical therapies.[6]

Baboush et al.[7] found that splenomegaly, mediastinal mass, T-cell phenotype, central nervous system involvement, lactate dehydrogenase ≥2000 U/L, and white blood count (WBC) ≥20 × 10^9/L ($p<0.001$) were predictors of TLS. Cairo et al.[8], on behalf of the TLS Expert Panel, developed guidelines to assign low, intermediate, and high risk to patients with cancer at risk for TLS. Risk factors include biological evidence of laboratory TLS (LTLS), high tumor proliferation rate, bulk and stage of malignant tumor, and renal impairment and/or involvement at the time of TLS diagnosis.

Analyzing independent risk factors for the development of TLS in children with ALL at the first stage of induction chemotherapy is crucial to prompting stronger interventions and closer monitoring of high-risk patients in order to improve patient survival. Therefore, the objective of our study was to identify risk factors for TLS in children with ALL.

METHODS

Research design

This was a retrospective cross-sectional study from medical record data of children aged 0 to 18 years with ALL in the pediatric hematology oncology ward of Dr.Soetomo General Academic Hospital from January to December 2021.

Research subjects

All new cases of ALL that were hospitalized in the pediatric hematology oncology ward were enrolled in the study. Tumor lysis syndrome is stated to occur in two forms: laboratory and clinical. Laboratory TLS is defined when two or more of the following biochemical abnormalities are present: (i) hyperuricemia (uric acid levels > normal values according to age); (ii) hyperkalemia (potassium >6mEq/L; (iii) hyperphosphatemia (phosphate >6.5mg/dL); (iv) hypocalcemia (calcium <7mg/dL). Meanwhile, clinical TLS includes an increase in serum creatinine of 1.5x standard value depending on age, the presence of heart attacks, sudden death, and seizures, or having more than one clinical symptom accompanied by laboratory abnormalities.[9]

Data collection

Patients with incomplete medical record data were excluded. The characteristics of the patients were documented, and risk factors for TLS were analyzed, including age at initial diagnosis, nutritional status, leukocyte count at initial diagnosis, presence of organ infiltration, presence of mediastinal mass, uric acid, renal function according to the glomerular filtration rate (GFR), and type of chemotherapy regimen. Clinical markers of organ infiltration found by physical examination as well as by laboratory and radiological investigation were as follows: mediastinal mass on chest radiograph, hepatomegaly (palpable liver ≥3cm below the right costal margin), splenomegaly (palpable spleen ≥2 cm below the left costal margin), central nervous system involvement (blasts found on Gram staining of CSF), and renal involvement (renal enlargement on abdominal USG).

Data analysis

All data were analyzed using the statistical software program EZR version 1.55. Characteristic data was presented as tables of

frequency and percentage of variables. Bivariate analysis was conducted to investigate the association between each risk factor variable and evidence of TLS. Then, variables with a value of $p<0.25$ were included in the multiple logistic regression analysis with the backward method. A value of $p<0.05$ was declared to be significant. The magnitude of the TLS risk factor is expressed as the odds ratio (OR) and 95% confidence index (95% CI).

Ethical clearance

The ethical feasibility of the study was approved by the Health Research Ethics Committee (KEPK) of Dr. Soetomo General Academic Hospital under no. 0904/LOE/301.4.2/V/2022.

RESULTS

A total of 94 patients with new ALL met the criteria for inclusion in this study. Thirteen patients were excluded, consisting of 3 patients who died before completing chemotherapy, 4 patients with incomplete medical record data, and 6 patients who did not finish the chemotherapy protocol. The remaining 81 patients, including 27 (33.3%) with TLS, could be analyzed. Most of the study subjects were male (64.2%). The mean age of patients at the time of initial diagnosis of ALL was 6 years and 9 months, and the majority (77.8%) of patients were under 10 years old. The characteristics of the 81 subjects can be seen in Table 1. Based on clinical findings and laboratory abnormalities, 15 (55.6%) patients with TLS had spontaneous TLS, and 12 (44.4%) had chemotherapy-induced TLS.

Simple logistic regression analysis was carried out to determine the risk factors of TLS in children with ALL. Table 2 shows that the significant factors were chemotherapy protocol, presence of mediastinal mass, organ infiltration, leukocyte count at initial diagnosis, decreased renal function, and increased uric acid. Meanwhile, other variables were not proven to be significant risk factors for TLS. The adjusted OR analysis showed that the most significant factor of TLS was decreased renal function (OR 12.21; 95% CI 1.09-136.89; p=0.042), which means that the risk of TLS increases 12 times in patients with decreased renal function compared to patients without decreased renal function. This was followed by leukocyte count at initial diagnosis and organ infiltration. Meanwhile, the rest of the risk factors were not significant for TLS (Table 3).

DISCUSSION

This study showed that the prevalence of TLS was 33.3% in new cases of pediatric ALL in 2021. These data were similar to our data in 2018, which showed 31.7%.[1] This result is still comparable to the prevalence of TLS in pediatric hematologic malignancies worldwide, ranging from 19-42%.[3,10]

Fifteen out of 27 (55.6%) patients with TLS experienced spontaneous TLS. The results of this study differed from those of previous research by Naeem et al.[4] showing that chemotherapy-induced TLS (72%) is more common than spontaneous TLS. This difference could be caused by the higher mean leukocyte count in their study. "Spontaneous TLS" refers to TLS manifestations in patients without cytotoxic therapy. Spontaneous TLS is rare but can lead to more severe clinical results due to the lack of treatment benefits.[6,11,12]

Table 1. Characteristics of children with acute lymphoblastic leukemia (n=81)

Variable	n	%
Sex		
Male	29	35.8
Female	52	64.2
Age		
≤10 years	63	77.8
>10 years	18	22.2
Nutritional status		
Normal	39	48.1
Malnutrition	42	51.9
Chemotherapy Protocol		
High Risk	46	56.8
Standard Risk	35	43.2
Mediastinal Mass		
Yes	5	6.2
No	76	93.8
Organ Infiltration		
Yes	26	32.1
No	55	67.9
Leukocyte count (/mm^3)		
<50.000	66	81.5
≥50.000	15	18.5
Renal function		
Normal	70	86.4
Decreased	11	13.6
Uric acid		
Normal	51	63.0
Increased	30	37.0

Data presented as n (%)

Table 2. Simple logistic regression analysis of risk factors for tumor lysis syndrome

Variable	TLS (+) (n = 27)	TLS (-) (n = 54)	OR	95% CI		p-value
Age						
≤10 years	19 (30.2)	44 (69.8)	0.54	0.18	1.58	0.257
>10 years	8 (44.4)	10 (55.6)				
Nutritional status						
Normal	13 (33.3)	26 (66.7)	1.00	0.39	2.52	1.000
Malnutrition	14 (33.3)	28 (66.7)				
Chemotherapy protocol						
High Risk	23 (50.0)	23 (50.0)	7.75	2.35	25.49	<0.001*
Standard Risk	4 (11.4)	31(88.6)				
Mediastinal Mass						
Yes	4 (80.0)	1 (20.0)	9.21	1.97	87.04	0.04*
No	23 (30.3)	53 (69.7)				
Organ Infiltration						
Yes	16 (100.0)	0 (0.0)	6.40	2.28	17.92	<0.001*
No	11 (20.0)	44 (80.0)				
Leukocyte count (/mm^3)						
<50.000	15 (22.7)	51 (77.3)	13.60	3.38	54.60	<0.001*
≥50.000	12 (80)	3 (20.0)				
Renal function						
Normal	17 (24.3)	53 (75.7)	31.17	3.71	261.50	<0.001*
Decreased	10 (90.9)	1 (9.1)				
Uric Acid						
Normal	8 (15.7)	43 (84.3)	9.28	3.22	26.76	<0.001*
Increased	19 (63.3)	11 (36.7)				

Data presented as n (%), OR = odds ratio; CI : confidence interval; p-value<0.05 means that the variable is statistically significant

Xue et al.[5] showed that age at the time of first diagnosis was a risk factor for TLS and that the age group under one year had the highest risk of TLS. This study also showed that the age group of >10 years has a lower risk than the age group of < one year but is still more at risk than the age group of 1-10 years. In our study, age at the initial diagnosis was not a risk factor because no data samples were obtained from patients aged <1 year, therefore risk factor analysis could not be performed in this age group.

Our study showed that nutritional status was not significantly proven to be a risk factor for TLS. This result contradicts a previous study in Pakistan showing that malnutrition substantially increases the mortality rate of TLS.[13] Weight loss, especially loss of muscle mass in ALL patients during chemotherapy, causes patients to easily fall into a state of dehydration. The excretion of toxic substances (potassium, phosphate, and uric acid) from the breakdown of cancer cells by the kidneys is not optimal, thereby putting them at risk of TLS.[14] These differences might be caused by the method of determining nutritional status in our study, which was based on measuring body weight/height. In children with ALL, the ideal determination of nutritional status is by measuring the circumference of the upper arm. However, most of the medical records did not have upper arm circumference data.

Table 3. Multiple logistic regression analysis of risk factors for tumor lysis syndrome

Variable	Adjusted OR	95% CI		p-value
Chemotherapy protocol	1.61	0.32	8.04	0.559
Mediastinal Mass	2.03	0.10	39.39	0.639
Organ Infiltration	5.42	1.45	20.27	0.012*
Leukocyte count	8.70	1.67	45.13	0.010*
Renal function	12.21	1.09	136.89	0.042*
Uric Acid	3.85	0.97	14.81	0.054

*p-value<0.05 means that the variable is statistically significant;OR : Odds Ratio; CI : confidence interval

The leukocyte count at the time of initial diagnosis was shown to be a significant risk factor for TLS. Xue et al.[5] showed a higher proportion of children with acute T-cell lymphoblastic leukemia in the leukocyte group >50,000/mm^3. The greater the number of leukocytes, the faster the cell proliferation and the more cells that lyse and release toxic metabolites such as phosphate that eventually binds to calcium and precipitates as calcium phosphate in the kidneys. A higher leukocyte count also indicates a high proliferation of cancer cells. A high leukocyte count increases the risk of spontaneous TLS and chemotherapy-induced TLS.[5] Patients with hyperleukocytosis (leukocytes >100,000/mm^3) must be treated with hyperhydration, with 3000 mL/m^2 body surface area to avoid the risk of leukostasis and TLS.[6,9]

In simple and multiple logistic analyses, organ infiltration was a significant risk factor for TLS in ALL children. Patients with large tumor masses, extensive metastases, and bone marrow and kidney involvement were more at risk of TLS. The greater the cancer mass or the faster the cancer cell proliferation, the greater the risk of massive cell lysis when administering induction chemotherapy. Hepatomegaly, splenomegaly, and nephromegaly may indicate tumor infiltration of these organs. Kidney infiltration or obstruction of the urinary tract by tumor cell infiltration may decrease the rate of excretion of toxic metabolites resulting from tumor cell breakdown, thereby increasing the risk of TLS.[15,16]

Increased uric acid level was not a significant risk factor for TLS in multivariate analysis but tended to increase the incidence of TLS. In our study, hyperuricemia was the most common laboratory abnormality in 16 out of 27 (66%) patients. The same result was found in the research by Naeem et al.[4] in Pakistan, showing that hyperuricemia is also one of the most common laboratory characteristics in patients with laboratory TLS (82.4%). The destruction of tumor cells releases purine nucleic acids, which are metabolized to xanthin; then, xanthin is metabolized to uric acid by the enzyme xanthin oxidase and causes hyperuricemia. When the concentration of uric acid in the renal tubules increases, uric acid crystals are deposited in the kidney, obstructing the renal tubules and causing nephropathy. The kidneys cannot excrete the destroyed tumor cells, which will accumulate in the body and result in severe serious manifestations of TLS.[2,17,18] The British Committee for Standards in Hematology recommend administering allopurinol as prophylaxis for TLS during the induction phase up to 7 days after chemotherapy administration.[14] Allopurinol, a xanthin oxidase inhibitor, acts by inhibiting the conversion of hypoxanthin to xanthin and xanthin to uric acid. Allopurinol does not play a role in destroying previously formed uric acid; therefore, allopurinol administration is more effective in preventing TLS.[6,14]

Multiple logistic regression analysis showed that the main factor that influenced the appearance of TLS was decreased renal function. These results were similar to those of a previous study, indicating that the incidence of TLS was significantly affected by acute kidney injury.[1] The study by Naeem et al.[2] also obtained similar results, showing significant changes in mean serum creatinine levels in patients with TLS at D0, D3, and D7 after chemotherapy. However, decreased renal function may result from other causes, such as kidney tumor infiltration, obstructive uropathy caused by tumors, nephrotoxic drugs, leukostasis, sepsis, or previous hypovolemia and renal dysfunction conditions. The most common cause of kidney function impairment in patients with TLS is the accumulation of uric acid crystals in the renal tubules.[17,18] In our study, there were no data explaining the causes of decreased kidney function in the patients; therefore, it could not be analyzed whether reduced kidney function is a risk factor for TLS or is a symptom of TLS that occurs in our patients. Evaluation of decreased urine output and early intervention in nephrology are essential in treating TLS rather than administration of loop diuretics.[8,19,20]

Our study showed that the type of chemotherapy protocol administered to patients was not a risk factor for TLS in children with ALL. One difference between standard-risk and high-risk chemotherapy regimens is the choice of the type of corticosteroids administered. Despite this result, the British Committee on Standards in Haematology Guidelines recommends that all patients in the high-risk group receive continuous intravenous hydration during the induction phase to optimize renal function and prevent acidosis.[14]

This study used secondary data from medical records, therefore data incompleteness was inevitable. However, the results can be used to determine the risk factors for TLS, such that clinicians can prevent TLS in pediatric ALL. This result emphasizes how crucial it is to include renal function data by measuring the GFR, leukocyte count at initial diagnosis, and organ infiltration in the risk assessment and management of TLS in

childhood ALL. Prospective and multicenter studies are required to develop a low, intermediate, and high-risk TLS classification in childhood ALL.

CONCLUSIONS

Reduced renal function was the highest risk factor for TLS in pediatric ALL Recognizing the patients at risk of developing TLS is essential, and so is the prophylactic treatment. Multicenter data collection on patient characteristics, clinical results, and supporting examinations should be carried out in more detail to discover more risk factors for TLS in pediatric patients with ALL.

Conflict of Interest

Competing interests: No relevant disclosures.

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Author Contributions

MRA was responsible for conceptualization, methodology, manuscript supervision, validation, and clinical review. AH was responsible for conceptualization, methodology, data sampling, and analysis. AC was responsible for conceptualization, methodology, and data analysis. MCSL supervised and validated the manuscript, and reviewed the clinical aspects. APAA was responsible for data collection and writing of the manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

Upon reasonable request, the corresponding author will provide the raw data supporting the study's conclusions.

Declaration of Use of AI in Scientific Writing

The authors declare that they did not use artificial intelligence (AI) in the writing of this manuscript.

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