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Original Article

Risk Factors for Hepatotoxicity From L-Asparaginase Chemotherapy In Children With Acute Lymphoblastic Leukemia

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ABSTRACT

Introduction: L-asparaginase chemotherapy often causes hepatotoxicity and affects complete remission in pediatric acute lymphoblastic leukemia (ALL). This study aims to investigate the risk factors that affect the incidence of hepatotoxicity caused by L-asparaginase chemotherapy in ALL children. **Methods:** An observational study with prospective sampling was conducted at Dr. Soetomo Hospital, Surabaya. The inclusion criteria included ALL children aged 1-18 years, undergoing ALL Induction phase chemotherapy based on the 2018 Indonesian Children's ALL protocol as evidenced by bone marrow aspiration, receiving L-asparaginase chemotherapy, and obtaining written consent from parents or guardians. Each child had 3 ml of blood drawn from a peripheral vein to assess their complete blood count, alanine transaminase (ALT) levels, and albumin level. **Results:** Thirty-two children with ALL were collected. Two of them were excluded due to allergic reaction and enable to continue the L-asparaginase chemotherapy. Thirty of them were eligible participants. Approximately 53.3% of ALL children aged ≤ seven years. Fourteen (47%) children with ALL were included in the standard-risk group and 16 (53%) of them included high-risk group. There were significant differences in ALT levels between the four stages of observation (p=<0.001). Twenty-two ALL children had hepatotoxicity (73.3%), while 8 had non-hepatotoxicity (26.7%). Two risk factors had a significant influence on the occurrence of hepatotoxicity due to L-asparaginase chemotherapy including age and hypoalbuminemia (p=0.045, p=0.028). **Conclusion:** Age and hypoalbuminemia were the risk factors that might affect the incidents of hepatotoxicity. Clinical monitoring before and after treatment needs to be done to prevent poor outcomes.

Key words: Acute lymphoblastic leukemia, Hepatotoxicity, L-asparaginase, Children.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common hematological malignancy in children, with a mortality of up to 50% in 1975 and 2010 decreased to 20-30%, especially since combination chemotherapy.[1,2] Combination chemotherapy containing L-asparaginase has been shown to increase survival rates by up to 71% compared to without L-asparaginase with a rate of only 31%.[1] L-asparaginase added to the initial regimen (dexamethasone and vincristine) can improve complete remission in up to 95% of children with ALL.[1,2] Nonetheless, L-asparaginase is the most common cause of hepatotoxicity among other chemotherapeutic agents, causing delays in chemotherapy and affecting complete remission in children with ALL.[3] Failure to receive L-asparaginase doses during the induction phase and the appearance of toxic effects are associated with poor outcomes in children with ALL.[1] Various risk factors can increase the incidence of L-asparaginase-related hepatotoxicity including the ALL risk group and L-asparaginase accumulation doses.[4]

Age greater than 10 years, body mass index, ALL risk categories, drug accumulation dose, and hypoalbuminemia are some of the factors that can enhance the likelihood of hepatotoxicity as a result of L-asparaginase treatment. The interplay of changes in growth hormones during adolescence and other factors is the multifactorial mechanism by which teenage age contributes to the formation of liver problems.[5] A body mass index (BMI) of more than or equal to 2 m^2 increases the risk of hepatic metabolic diseases.[6] L-asparaginase in the body will be metabolized in the liver by cytochrome P450 (CY450). The impact of L-asparaginase administration will cause asparagine deficiency which affects protein synthesis activity and inhibition of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis occurs. Depletion of arginine and glutamine levels will change nicotinamide acetyl dehydrogenase levels which are associated with the inhibition of protein synthesis which ultimately induces damage to hepatocyte cells.[7]

Toxicity of L-asparaginase grades 3 and 4 is associated with poor clinical outcomes which lead to increased mortality and morbidity, affect the quality of life and increase the length of stay. There have not been many studies on the factors that affect the incidence of hepatotoxicity caused by L-asparaginase chemotherapy in Indonesia. The prevalence of hepatotoxicity brought on by L-asparaginase treatment in children with ALL has never been investigated at the Tertiary Referral Hospital in Surabaya. For L-asparaginase therapy to be effective and prevent acute toxicity, it is necessary to identify the variables that affect the incidence of hepatotoxicity caused by L-asparaginase chemotherapy in children with ALL. This will help the children with ALL achieve complete remission and prevent relapse.

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MATERIALS AND METHODS

The research was conducted in an analytic observational study with prospective sampling. Recruitment of research participants was carried out from March to September 2022. The research participants in this study were children with ALL who underwent induction phase chemotherapy and received L-asparaginase according to the 2018 Indonesian Children's ALL protocol,[8] at the Pediatric Ward, Division of Hematology-Oncology, Department of Child Health, Dr. Soetomo General Academic Teaching Hospital, Surabaya. The inclusion criteria for this study included children with ALL types L1 and L2 aged 1-18 years, children undergoing ALL Induction phase chemotherapy based on the 2018 Indonesian Children's ALL protocol as evidenced by bone marrow aspiration, receiving L-asparaginase chemotherapy, and obtaining written consent from parents or guardians to participate by signing an informed consent form after being given information regarding the research stages. We excluded participants with the following criteria including children with ALL who had elevated serum Alanine aminotransferase (ALT) levels more than the upper threshold of normal before being given L-asparaginase chemotherapy and children who died before the start of L-asparaginase chemotherapy. Criteria for dropping out in this study included children with ALL who refused to continue chemotherapy, children with allergic reactions and other adverse events besides an increase in serum ALT which causes the dose of L-asparaginase to be adjusted or stopped, children with ALL who have elevated serum ALT levels of more than 5 times the upper normal threshold while receiving L-asparaginase chemotherapy, and children who died before L-asparaginase chemotherapy was completed.

The research flow is shown in Figure 1. Children with ALL were identified according to the inclusion and exclusion criteria, then the parents or guardians of children with ALL were given information and education regarding the research series. We collected data on patient characteristics in data collection sheets including age at diagnosis, gender, ethnicity, nutritional status, and grouping children with ALL into standard risk and high risk. In the first observation, which was the participant's observation before receiving L-asparaginase chemotherapy, each child was examined by a pediatrician. Children who meet the requirements for L-asparaginase chemotherapy will be ordered chemotherapy drugs from the pharmaceutical production department. In children with standard-risk ALL, L-asparaginase will be given a total of six times by administering L- asparaginase 7500 IU/m^2 dissolved with 0.9% 100 ml NaCl infusion fluid used up in one hour every two days. Children with high-risk ALL, L-asparaginase will be given a total of eight times by administering L-asparaginase 7500 IU/m^2 dissolved with 0.9% NaCl infusion 100 ml finished in one hour every three days. At each stage of observation, children with ALL will

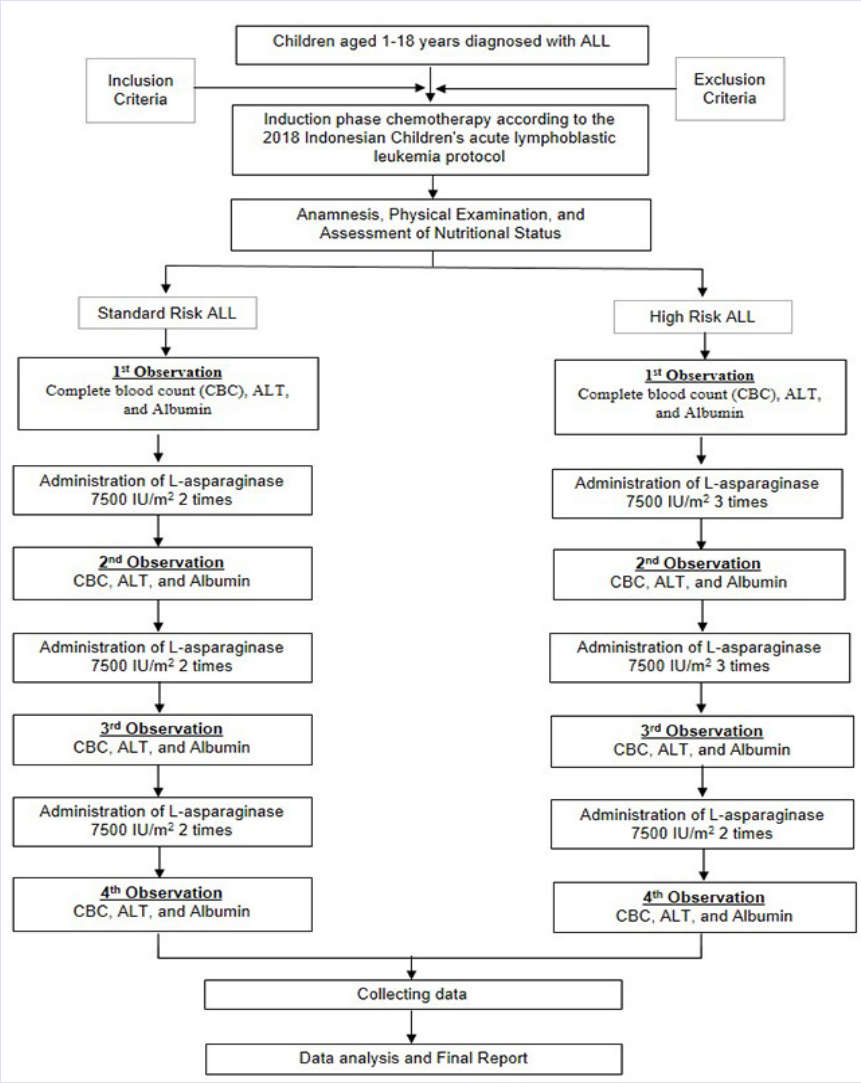

Figure 1: Research flow and stage.

go through routine physical examinations and complete blood count, serum albumin, and ALT levels for four observations. Pediatric patients with ALL are categorized as experiencing hepatotoxicity if one of the observations has ALT levels > 45 U/L.

Laboratorium examination

Each child with ALL who met the inclusion criteria had 3 ml of blood taken *via* a peripheral vein using a 5 ml disposable syringe brand Terumo and a 23.5 Gauss needle. Blood is placed in BD Vacutainer® ethylenediaminetetraacetic acid (EDTA) K2 tubes for complete blood count and a tube with a yellow cap containing acid-citrate-dextrose (ACD) for albumin level examination. The laboratory tests included a complete blood count, ALT level, and serum albumin level at each of the 4 stages of observation. The vacuum tube was then taken and examined at the Clinical Pathology Laboratory, Central Diagnostic Building, Dr. Soetomo General Academic Teaching Surabaya.

Data analysis

Descriptive analysis was performed using statistical measures including mean, standard deviation, median, and frequency distribution tables. Data analysis was performed using IBM SPSS Statistics Version 25 and Microsoft Office Excel. The Friedman test was carried out to assess differences in ALT levels at each observation. This test is used because there is one observation period with a significance value of p-value below 0.05, so the ANOVA test cannot be used. A binary logistic regression test for each risk factor for the occurrence of hepatotoxicity was used to analyze the factors that affect the incidence of hepatotoxicity caused by L-asparaginase treatment in children with ALL. A multivariate analysis will be performed to determine which risk factors are most associated with the development of hepatotoxicity following L-asparaginase treatment.

Ethical clearance

The ethical clearance of this study has been tested and approved by the Clinical Research Unit, Dr. Soetomo General Academic Teaching Surabaya No. 0390/KEPK/III/2022 which was issued on March 7, 2022.

RESULTS

A total of 32 children diagnosed with ALL will receive L-asparaginase chemotherapy during the study period. Two children with ALL were eliminated from the study because during the L-asparaginase chemotherapy they had an allergic reaction and could not continue to complete L-asparaginase chemotherapy. The number of participants who could be examined and analyzed in this study was 30 children. The characteristics of the patients are shown in Table 1. The number of study subjects was 30 with a proportion of age ≤ 7 years more (53.3%). A total of 14 (47%) children with ALL were included in the standard-risk group and 16 (53%) of them included high-risk group. Table 2 shows the mean and median values for laboratory tests at the beginning of the observation before starting chemotherapy. Analysis of the ALT level assessment during the four observation periods is shown in Table 3. Figure 2 presents a diagram of the average ALT values in the fourobservation periods. pre-chemotherapy ALT levels had an average of 34.11 ± 8.39 U/L, after L-asparaginase chemotherapy the 2nd observation ALT levels increased to 67.88 ± 36.74 U/L, the 3rd observation ALT levels were 53.99 ± 20.53 U/L. In the 4th observation, ALT levels had a higher average value with an average value of 121.49 ± 284.48 U/L. There were significant differences in ALT levels between the four stages of observation (p=<0.001). The number of participants who experienced the most increase in ALT level was from the first observation to the 2nd observation, which was 86.7%, followed by 66.7% from the 3rd observation to the 4th observation.

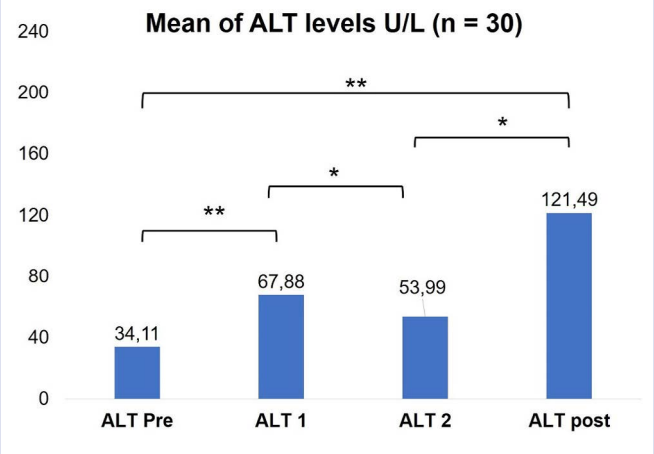

Figure 2: The mean of ALT levels in four stage of observations.

Table 1: The characteristic of study's participants.

Parameter	n (%)
Age (year)	
≤ 7	16 (53.3)
> 7	14 (46.7)
Sex	
Male	19 (63.3)
Female	11 (36.7)
Ethnicity	
Java	28 (93.3)
Madura	2 (6.7)
ALL risk Group	
Standard risk group	14 (47)
High risk group	16 (53)
Nutritional status	
Obesity	6 (20)
Overweight	1 (3.3)
Normal	18 (60)
Underweight/wasted	5 (16.7)
ALL morphology	
L1	29 (97)
L2	1 (3)
Hemoglobin (g/dL)	
<10	18 (60)
≥10	12 (40)
Leucocyte (mm^3)	
<4,000	4 (13.3)
4,000 - <10,000	21 (70)
≥ 10,000	4 (16.7)
Platelets (mm^3)	
< 100,000	17 (56.7)
≥100,000	13 (43.3)
1st observation albumin level (g/dL)	
< 3.0	21 (70)
≥ 3.0	9 (30)

Note: Data was presented as number (percentage); Abbreviations: ALL, Acute lymphoblastic leukemia

At the end of the observation, it was found that 22 children with ALL had hepatotoxicity (73.3%), while 8 had non-hepatotoxicity (26.7%). In this study, the average accumulated dose of L-asparaginase was 43,887.73 ± 21,230.27 with a median value of 37,050 (7,200 – 90,000). No significant relationship was found between the accumulated dose of the drug and the incidence of hepatotoxicity (p=0.099). Table 4 shows the analysis of the effect of each risk factor on the presence of hepatotoxicity. Two risk factors had a significant influence on the

Table 2: Laboratory examination at the beginning of the observation.

Parameter	Mean ± SD	Median (min-max)
Hemoglobin (g/dL)	9.51 ± 1.09	9.50 (7.50 - 12)
Leucocyte (mm^3)	8,560 ± 8,427	6,850 (2,300 – 50,000)
Platelets (mm^3)	99,220 ± 37,320	98,000 (55,000 – 201,000)
Albumin (g/dL)	2.97 ± 0.28	3.00 (2.5 – 3.5)

Abbreviations: SD, Standard Deviation; Min, minimun; Max, Maximum

Table 3: The differences in ALT values at the 4 stages of observation.

Observation	ALT level Mean ± SD	p-value	p-value total
1st Observation	36.11 ± 8.39	-	<0.001*
2nd Observation	67.88 ± 36.76	<0.001*[a]	
3rd Observation	53.99 ± 20.53	0.003*[b]	
4th Observation	121.49 ± 284.48	0.002*[c]	

Friedman test was used; *, a p-value below 0.05 was significant; [a], difference test between 1st and 2nd observations; [b], difference test between 2nd and 3rd observations; [c], difference test between 3rd and 4th observations

Table 4 Analysis of risk factors for hepatotoxixty.

Risk factors	Hepatotoxicity		RR (95% CI)	p-value
	Yes	No		
Age (year)				
≤ 7	9	7	10.11 (1.054-97.00)	0.045*
> 7	13	1		
Sex				
Male	15	4	0.467 (0.090-2.432)	0.366
Female	7	4		
Nutritional status				
Obesity	6	0		0.999
Overweight	1	0	0.230 (0.173-1.254)	0.999
Normal	12	6		0.782
Underweight/wasted	3	2		0.995
ALL risk Group				
Standard risk group	16	0	1.167 (0.269-5.054)	0.998
High risk group	6	8		
Accumulated dose of drug (IU/m^2)				
≤ 37.000	9	6	0.131 (0.708-2.531)	0.113
> 37.000	13	2		
Albumin level (mg/dl)				
<3	18	3	7.5 (1.24-45.15)	0.028*
≥ 3	4	5		

Binary logistic regression was performed as appropriate

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; ALL, Acute lymphoblastic leukemia; *, a p-value < 0.05 was statistically significant

occurrence of hepatotoxicity due to L-asparaginase chemotherapy including age and hypoalbuminemia (p=0.045, p=0.028). It can be concluded that children with ALL who are older than 7 have a 10-fold greater risk of developing hepatotoxicity. Meanwhile, in this study, hypoalbuminemia in pediatric ALL patients increase the risk of hepatotoxicity by 7.5 times. In multivariate analysis, age and hypoalbuminemia did not effect on the incidence of hepatotoxicity due to L-asparaginase chemotherapy (p=0.100 and p=0.094).

DISCUSSION

This study involved 30 children with ALL aged 1-18 years who received L-asparaginase chemotherapy and met the inclusion criteria. The proportion of participants in this study was ≤ 7 years old (53.3%) and > 7 years old. A study in Tehran[9] showed that the mean age of children with ALL was 5.5 years and in Brazil,[10] the average age of children at initial diagnosis was 6.3 ± 0.5 years.[11] An epidemiological study conducted by Kakaje *et al.*,[11] on 202 children with ALL, found a higher proportion of boys with ALL (60.9%) compared to girls. The incidence of ALL cases in children in Indonesia alone is around 4.32 per 100,000 children with a higher incidence of boys than girls (2.45 per 100,000 children).[12] In this study, 53% of children were included in the high-risk group. A study stated that treatment of high-risk ALL patients is given a multiagent chemotherapy regimen, followed by hematopoietic stem cell transplantation (HSCT).[13] The ALL risk group is one of the factors that can increase the occurrence of liver disorders due to L-asparaginase administration.[5]

Laboratory tests in this study showed that the average hemoglobin level was 9.51 ± 1.09 g/dL. In this study, almost all participants, namely 18 children with ALL, had a hemoglobin level <10 g/dL. The results of this study are consistent with a study in which the majority (62%) of ALL patients in children in the induction phase had hemoglobin levels of 5-10 g/dL.[14] It was also explained that most of the subjects had platelet levels between 50,000 – 150,000 mm^3. Whereas in this study, more than half of the sample (56.7%) had platelet counts between <100,000 mm^3 with an average platelet level of 99,220 (37,230) mm^3. A study by Schmidt *et al.*[15] (2021) showed that hemoglobin concentration was not significantly related (p=0.867) to the incidence of hepatotoxicity due to L-asparaginase therapy in ALL patients. Approximately 70% had a leukocyte count of 4,000 - <10,000 mm^3 and only five children had a leukocyte count ≥ 10,000 mm^3. This is in line with a study conducted by Conter *et al.*[16] that the number of patients with early T-cell acute lymphoblastic leukemia with a white blood cell count lower than 20,000 cells per L was 26 (53%).[16]

L1 lymphoblast morphology dominated in this investigation. According to a prior study, up to 80% of children have L1 lymphoblast morphology with cells that are small and uniform in size, with clear, slightly bluish cytoplasm, and nuclei that are regularly shaped.[14] Larasati *et al.*[17] (2016) stated that the majority of ALL children were dominated by ALL L1 (73.5%) and as many as 9 children with ALL L2. Differences in lymphoblast morphology did not affect the incidence of hepatotoxicity related to L-asparaginase chemotherapy.[17] The majority of albumin levels before L-asparaginase chemotherapy in this study were <3.0 g/dL. A study in Sudan evaluating albumin levels before L-asparaginase chemotherapy found that the initial albumin level in 80 children with ALL was 3.6 g/dL.[18] Albumin levels are associated with reduced event-free survival in pediatric cancer patients.[19] In addition, hypoalbuminemia is also associated with outcomes that are inferior to normal albumin levels in pediatric patients with cancer. However, a cohort study found that hypoalbuminemia before starting chemotherapy was not associated with relapse and overall survival.[20]

During L-asparaginase chemotherapy, 86.7% experienced an increase in ALT levels at the 2nd observation. The same thing can also be seen in the 3rd to 4th observation where there is an increase in ALT levels in 66% of children. However, this is different from the 2nd observation where ALT levels compared to the 3rd observation decreased by 80% from the 2nd observation to the 3rd observation. A study stated that evaluating liver function before and after administration of L-asparaginase chemotherapy in ALL children found that out of 80 study participants had ALT levels before chemotherapy with an average value of 85 IU/L and after chemotherapy, there was an increase of 111 IU/L.[18] ALT levels in children between before and after induction phase chemotherapy differed significantly, but not significantly between two or four weeks. This suggests that exposure to chemotherapeutic drugs triggers the production of ALT levels but increasing the cumulative dose of drugs may not increase ALT levels.[21] The use of L-asparaginase in ALL causes quite frequent abnormalities in liver function and may in some cases require discontinuation of treatment. One of the characteristics of impaired liver function after the administration of L-asparaginase is a slight increase in ALT levels. Even cholestatic or hepatocellular

liver injury with or without steatosis has been reported. However, L-asparaginase hepatotoxicity in most cases is mild and regressive and rarely causes jaundice. Therefore, to prevent this side effect, it is recommended to perform liver function tests before chemotherapy and at least once a week during L-asparaginase therapy and discontinue treatment if significant changes occur and avoid giving L-asparaginase to patients who already show abnormal values. Patients who have increased ALT levels before treatment require continuous monitoring.

Hepatotoxicity is the second most common case as an effect of L-asparaginase therapy in ALL patients with a prevalence of 19.4% with a severity level of 62.5% having hepatotoxicity greater than equal to 3, as many as 37.5% having hepatotoxicity below grade 3, even 12.5% experiencing hepatotoxicity grade 5 with fulminant liver failure and death.[15] In this study, the prevalence of hepatotoxicity due to L-asparaginase chemotherapy in pediatric patients with ALL was 73.3% with the hepatotoxicity category used being a cut-off > 45 U/L equivalent to grade 1 hepatotoxicity based on the Common Terminology Criteria for Adverse Events (CTCAE) 2017.[3] Management of hepatotoxicity associated with L-asparaginase chemotherapy depends on the severity of the hepatotoxicity. If grade 1 and 2 hepatotoxicity occurs, the patient will be subject to clinical monitoring and L-asparaginase can still be continued. The condition of grade 3 and 4 hepatotoxicity needs intensive monitoring. In grade 3 with ALT levels > 5-20 times the upper limit of normal value, then the administration of L-asparaginase can be delayed until the minimal degree of hepatotoxicity has entered grade 3. If the toxicity reaches grade 4 with ALT levels more than 20 times the upper limit of normal value then it can be considered to stop giving L-asparaginase permanently or continue L-asparaginase therapy with close monitoring if the hepatotoxicity does not return to at least grade 2 within 1 week.

In this study, age was significantly associated with the incidence of hepatotoxicity in children with ALL who received L-asparaginase chemotherapy. The results of this study are also in line with a study stated that age is significantly associated with the incidence of grade 3-4 hepatotoxicity due to administration of L-asparaginase.[22] However, another study showed that the age factor did not significantly cause hepatotoxicity in ALL patients who received asparaginase, but patients who experienced hepatotoxicity tended to be older than those who did not experience toxicity.[6,23] A study reported that hepatotoxicity due to L-asparaginase chemotherapy is related to older age.[24] Obesity was identified as a predictor of hepatotoxicity where obese children have a 2.18-fold risk of developing hepatotoxicity during therapy. In addition, this study also stated that overweight and obesity in leukemia patients have the potential to provide bad interactions during therapy as evidenced by the high prevalence of hepatotoxicity in this group.[25,26]

The proportion of the high-risk group (53%) was higher than the proportion of the standard-risk group, even though the ALL-risk group was not a risk factor for hepatotoxicity because the high-risk group had no cases of non-hepatotoxicity. This study was also supported by the research of Schmidt *et al.*[15] (2021), which stated that high-risk ALL chemotherapy was not significantly associated (p=0.239) with the incidence of hepatotoxicity due to L-asparaginase therapy in pediatric patients with ALL.[15] The incidence of hepatotoxicity caused by L-asparaginase chemotherapy in children with ALL was not related to the drug accumulation dose factor in this study either; however, a different study suggested that hepatotoxicity caused by L-asparaginase chemotherapy was related to higher doses and more intense dosing schedules.[24] The dose given to patients needs to be monitored for L-asparaginase activity levels to identify patients with suboptimal activity levels to adjust treatment.[4,27,28,29]

Hypoalbuminemia is a factor influencing the incidence of hepatotoxicity due to L-asparaginase chemotherapy in children with ALL (p=0.028). A study reported that hepatotoxicity due to L-asparaginase therapy is related to low albumin factor, observation of hypoalbuminemia in ALL patients with malnutrition and reflecting the capacity of protein synthesis in the liver proves that L-asparaginase causes liver stress due to depletion of glutamine, an essential amino acid required for protein synthesis.[6] This study's drawback is limited of participants from the control group. However, at Dr. Soetomo General Academic Teaching Hospital Surabaya, this study is the first to examine risk factors for hepatotoxicity caused by L-asparaginase treatment.

CONCLUSION

The prevalence of hepatotoxicity due to L-asparaginase chemotherapy in children with ALL is 73.3%. The risk factors that have an influence on the incidence of hepatotoxicity in children with ALL according to bivariate analysis are age and incidence of hypoalbuminemia. Due to the significant risk of hepatotoxicity in this situation, clinicians should be cautious when administering L-asparaginase drug doses to children receiving treatment for ALL. Additional guidelines for the management of children receiving chemotherapy for ALL should be established. In children with ALL, regular ALT level monitoring is also necessary. A larger, multicenter study is advised to collect more comprehensive information on the hepatotoxicity of L-asparaginase treatment.

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DISCLOSURE

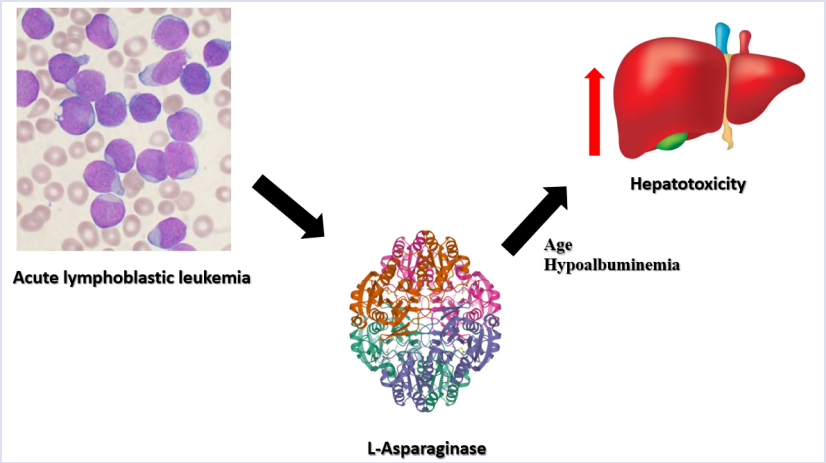
The author reports no conflicts of interest in this work.

REFERENCES

1. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, *et al.* Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012;30(14):1663-9.
2. Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and Trends of Pediatric Acute Lymphoblastic Leukemia - United States, 2001-2014. MMWR Morbid Mortality Weekly Rep. 2017;66(36):950-4.
3. Kamal N, Koh C, Samala N, Fontana RJ, Stolz A, Durazo F, *et al.* Asparaginase-induced hepatotoxicity: rapid development of cholestasis and hepatic steatosis. Hepatol Int. 2019;13(5):641-8.
4. Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leukemia lymph. 2016;57(4):748-57.
5. Bukowinski AJ, Burns KC, Parsons K, Perentesis JP, O'Brien MM. Toxicity of Cancer Therapy in Adolescents and Young Adults (AYAs). Seminars Oncol Nurs. 2015;31(3):216-26.
6. Rausch CR, Marini BL, Benitez LL, Elias A, Burke PW, Bixby D, *et al.* PEGging down risk factors for peg-asparaginase hepatotoxicity in patients with acute lymphoblastic leukemia (†). Leukemia lymph. 2018;59(3):617-24.
7. Egler RA, Ahuja SP, Matloub Y. L-asparaginase in the treatment of patients with acute lymphoblastic leukemia. J Pharmacol Pharmacotherap. 2016;7(2):62-71.

8. Hematology-Oncology Coordinating Unit of Indonesian Pediatric Society. Indonesian acute lymphoblastic leukemia protocol guidelines [Indonesian acute lymphoblastic leukemia protocol guidelines]: UKK Hematology; 2018.
9. Mehrvar A, Faranoush M, Asl AAH, Tashvighi M, Fazeli MA, Mehrvar N, *et al.* Epidemiological features of childhood acute leukemia at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran, Iran. Basic Clin Ca Res. 2015;7(1):9-15.
10. Lustosa de Sousa DW, de Almeida Ferreira FV, Cavalcante Félix FH, de Oliveira Lopes MV. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Revista brasileira de hematologia e hemoterapia. 2015;37(4):223-9.
11. Kakaje A, Alhalabi MM, Ghareeb A, Karam B, Mansour B, Zahra B, *et al.* Rates and trends of childhood acute lymphoblastic leukaemia: an epidemiology study. Sci Rep. 2020;10(1):6756.
12. Garniasih D, Susanah S, Sribudiani Y, Hilmanto D. The incidence and mortality of childhood acute lymphoblastic leukemia in Indonesia: A systematic review and meta-analysis. PLoS One. 2022;17(6):e0269706.
13. Mohseni M, Uludag H, Brandwein JM. Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications. Am J Blood Res. 2018;8(4):29-56.
14. Widiaskara IM, Permono B, Ugrasena IDG, Ratwita M. Luaran Pengobatan Fase Induksi Pasien Leukemia Limfoblastik Akut pada Anak di Rumah Sakit Umum Dr. Soetomo Surabaya. Sari Pediatri. 2016;12(2):128-34.
15. Schmidt MP, Ivanov AV, Coriu D, Miron IC. L-Asparaginase Toxicity in the Treatment of Children and Adolescents with Acute Lymphoblastic Leukemia. J Clin Med. 2021;10(19).
16. Conter V, Valsecchi MG, Buldini B, Parasole R, Locatelli F, Colombini A, *et al.* Early T-cell precursor acute lymphoblastic leukaemia in children treated in AIEOP centres with AIEOP-BFM protocols: a retrospective analysis. Lancet Haematol. 2016;3(2):e80-6.
17. Larasati MCS. Perbandingan Stratifikasi Risiko Leukemia Limfoblastik Akut dengan Penambahan Pemeriksaan Imunofenotiping Pada Luaran Kemoterapi Indonesian Protocol Acute Lymphoblastic Leukemia (ALL) 2013 Fase Induksi di RSUD Dr. Soetomo Surabaya [Comparison of Risk Stratification of Acute Lymphoblastic Leukemia with the Addition of Immunophenotyping Tests on the Outcomes of 2013 Indonesian Protocol Acute Lymphoblastic Leukemia (ALL) Chemotherapy in Induction Phase at RSUD Dr. Sutomo Surabaya]. 2016.
18. Jahalla A, Alameen AAM. Assessment of Liver Function Before and After L-Asparaginase Therapy in Acute Lymphoblastic Leukemia. European J Biomed. 2017;4(5):510-3.
19. McLean TW, Stewart RM, Curley TP, Dewsnup MY, Thomas SG, Russell TB, *et al.* Hypoalbuminemia in children with cancer treated with chemotherapy. Pediatr Blood Ca. 2020;67(2):e28065.
20. Schwartz GG, Tretli S, Vos L, Robsahm TE. Prediagnostic serum calcium and albumin and ovarian cancer: A nested case-control study in the Norwegian Janus Serum Bank Cohort. Cancer Epidemiol. 2017;49:225-30.
21. Mekonnen AT, Wondmeneh TG. Evaluation of liver function tests to identify hepatotoxicity among acute lymphoblastic leukemia patients who are receiving chemotherapy induction. Sci Rep. 2022;12(1):13215.
22. Christ TN, Stock W, Knoebel RW. Incidence of asparaginase-related hepatotoxicity, pancreatitis, and thrombotic events in adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen. J Oncol Pharm. 2018;24(4):299-308.
23. Schmiegelow K, Rank CU, Stock W, Dworkin E, van der Sluis I. SOHO State of the Art Updates and Next Questions: Management of Asparaginase Toxicity in Adolescents and Young Adults with Acute Lymphoblastic Leukemia. Clinical lymphoma, Myeloma Leukemia. 2021;21(11):725-33.
24. Douer D, Gökbuget N, Stock W, Boissel N. Optimizing use of L-asparaginase-based treatment of adults with acute lymphoblastic leukemia. Blood Rev. 2022;53:100908.
25. Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. Pediatr Blood Ca. 2018;65(3).
26. Meenan CK, Kelly JA, Wang L, Ritchey AK, Maurer SH. Obesity in pediatric patients with acute lymphoblastic leukemia increases the risk of adverse events during pre-maintenance chemotherapy. Pediatr Blood Ca. 2019;66(2):e27515.
27. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leukemia lymph. 2015;56(8):2273-80.
28. Mairuhu A, Andarsini MA, Setyoningrum RA, Cahyadi A, Larasati MCS, Ugrasena IDG, et al. Hospital acquired pneumonia risk factors in children with acute lymphoblastic leukemia on chemotherapy. Heliyon. 2021;7(6):1-4. https://doi.org/10.1016/j.heliyon.2021.e07209.
29. Cahyadi A, Ugrasena IDG, Andarsini MR, Larasati MCS, Aryati A, Arumsari DK. Relationship between bax and bcl-2 protein expression and outcome of induction phase chemotherapy in pediatric acute lymphoblastic leukemia. Asian Pac J Cancer Prev. 2022;23(5):1679-1685.

GRAPHICAL ABSTRACT



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