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Original Article

EFFECTS OF POST-CHEMOTHERAPY DRUGS ON THE LIVER FUNCTION TESTS IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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ABSTRACT

Objective: Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy, and its treatment, which involves multiple chemotherapy phases, can lead to hepatotoxicity. This study aimed to assess the differences liver function tests based on sociodemographic profile, as well as the prevalence of hepatotoxicity, in pediatric ALL patients undergoing chemotherapy.

Methods: A retrospective analytical observational study was conducted on 52 pediatric ALL patients treated between 2020–2022. Data on sociodemographic profile, chemotherapy phases, and liver function tests were collected from medical records. Chi-Square and Fisher's Exact tests were used for statistical analysis.

Results: The results indicated that pediatric ALL was more common in males (51.9%), with toddlers and adolescents both representing 34.6%. The maintenance chemotherapy phase was the most common (46.1%), and 84.6% of patients were classified as high-risk. There were no significant differences in bilirubin levels (total, direct, indirect) based on gender, age, chemotherapy phase, or ALL risk ($p>0.05$). AST levels varied by chemotherapy phase ($p<0.05$), but not by other factors. ALT levels differed by chemotherapy phase and ALL risk ($p<0.05$). Hepatotoxicity was rare, affecting only 3.9% of patients, with no significant relationship found between sociodemographic factors and hepatotoxicity ($p>0.05$).

Conclusion: This study highlights that liver function tests, particularly ALT and AST, varied significantly with chemotherapy phases and ALL risk but showed no differences based on gender or age. Hepatotoxicity was uncommon. Regular liver function monitoring during chemotherapy is important, especially for high-risk patients or those receiving intensive treatment.

Keywords: Acute lymphoblastic leukemia, Chemotherapy, Hepatotoxic, Bilirubin, AST, ALT

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is defined by the uncontrolled malignant growth of abnormal white blood cells (blast cells) within the bone marrow. This irregular and excessive proliferation disrupts normal blood cell functions, resulting in the development of leukemia symptoms. Children aged two to three years are about four times more likely to develop ALL compared to infants, and their risk is four to five times higher than that of children aged 10 y or older [1].

Hepatotoxicity is a frequently encountered and potentially serious side effect of many anticancer therapies. It is recognized as a relatively common yet potentially severe adverse reaction [2]. Symptoms of hepatotoxicity may include jaundice (yellowing of the skin, eyes, and mucous membranes due to increased bilirubin), itching, severe abdominal pain, nausea, vomiting, fatigue, weakness, continuous bleeding, rashes, swelling in the legs and feet, rapid abnormal weight gain, dark urine, and pale stools [3].

Hepatotoxicity refers to liver damage or impairment caused by an excess of drugs or foreign substances. Substances that induce liver injury are called hepatotoxins or hepatotoxicants, which can include overdoses of specific medications, industrial chemicals, natural toxins like microcystins, herbal remedies, and dietary supplements. Even drugs taken within therapeutic ranges can sometimes result in liver damage. Hepatotoxins is a harmful chemical that has the potential to harm the liver. It can lead to various clinical and histopathological signs of liver damage [1].

Liver injury due to hepatotoxicity can result from the direct action of the toxic substance, its reactive metabolites, or an immune response that affects liver cells, bile ducts, or blood vessels. The damage often presents with specific patterns of cell death in certain areas of the liver. Research on methotrexate-related hepatotoxicity showed that liver damage was caused by the activation of inflammatory pathways, increased pro-apoptotic mediators, and the formation of reactive oxygen species (ROS) [2]. Similarly, studies on doxorubicin-related hepatotoxicity revealed that ROS production, lipid peroxidation, upregulation of pro-apoptotic genes like Bax, and mitochondrial dysfunction contributed to liver injury [4].

Liver damage is typically detected through specific biochemical markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin. Elevated levels of these serum enzymes are key indicators of liver toxicity, while increased total and conjugated bilirubin levels reflect overall liver function. A significant increase in transaminase levels, combined with bilirubin levels exceeding twice the upper normal limit, is considered a concerning sign of hepatotoxicity [3]. AST and ALT are especially significant in detecting hepatotoxicity in patients, including those with ALL. Elevated levels of these enzymes can signal liver damage, which is crucial for ALL patients due to the intensive chemotherapy and medications they receive, often placing considerable strain on the liver. Monitoring these enzyme levels helps ensure early detection of liver issues, enabling timely interventions to mitigate damage and adjust treatment as needed [5]. This study aimed to examine the differences in liver function tests based on sociodemographic characteristics and determine the prevalence of hepatotoxicity in pediatric patients with ALL undergoing chemotherapy.

MATERIALS AND METHODS

Research design

This research was conducted in the medical records department of Dr. M. Djamil Hospital Padang. It is an analytical observational study utilizing retrospective data, where patient information from medical records collected in 2020-2022 was gathered using a total sampling method. The data collected included gender, age, chemotherapy phases and ALL risk level for the sociodemographic profile. In addition, this study also collected data on the levels of three types of bilirubin, AST and ALT. Hepatotoxicity was assessed based on the increase in ALT and total bilirubin levels.

Patient criteria

Data were collected from pediatric ALL patients (aged 0 – 18 y) who received chemotherapy during the period 2020-2022. This study excluded data from patients with malignancies other than ALL.

Data analysis

The sociodemographic profiles was presented descriptively in percentages. Then, the analysis of differences between sociodemographic profile and the bilirubin, AST and ALT profiles was conducted using the Chi-Square Test and Fisher's Exact Test. Likewise, hepatotoxicity was analyzed in relation to the sociodemographic profile using the same statistical tests.

Ethical approval

This study has received ethical approval from the Research Ethics Committee of Dr. M. Djamil Hospital Padang with Number: DP.04.03/D. XVI. XI/95/2024.

RESULTS

The study, conducted on 52 pediatric ALL patients at Dr. M. Djamil Hospital Padang, found that, according to table 1, the majority of the patients were male (51.9%). It was also observed that the toddler and adolescent age groups had an aqual distribution, each comprising 34.6% of the patients. Furthermore, during the study period, most patients were in the chemotherapy phase, with the maintenance phase being the most common (46.1%). Finally, high-risk cases (84.6%) were more prevalent than standard-risk cases.

Table 1: The sociodemographic profile of pediatric ALL patients

Sociodemographics	Number of patients (n=52)	Percentage (%)
Gender		
Female	25	48.1
Male	27	51.9
Age		
Toddler	18	34.6
Child	16	30.8
Adolescent	18	34.6
Chemotherapy phases		
Induction	18	34.6
Consolidation	7	13.5
Reinduction/intensification	3	5.8
Maintenance	24	46.1
ALL risk		
Standard	8	15.4
High	44	84.6

Table 2 illustrated the differences in the bilirubin profile of pediatric patients with ALL according to sociodemographic profile. The levels of total, direct and indirect bilirubin did not reveal significant differences based on gender, age, chemotherapy phases, and ALL risk (sociodemographic profile), with p-values>0.05 for each.

Table 2: Differences in the bilirubin profile of pediatric ALL patients based on the socio-demographic profile

Socio-	Total bilirubin level							Direct bilirubin level						Indirect bilirubin level					
demographics	BN	N	1	2	3	4	p-value	N	1	2	3	4	p-value	N	1	2	3	4	p-value
Gender																			
Female	4	18	2	1	0	0	0.339	9	5	9	2	0	0.112	20	4	1	0	0	0.278
Male	1	23	1	0	1	1		5	14	5	2	1		24	1	0	1	1	
Age																			
Toddler	1	15	2	0	0	0	0.195	7	4	7	0	0	0.067	15	2	0	0	0	0.613
Child	4	12	0	0	0	0		4	8	4	0	0		14	2	0	0	0	
Adolescent	0	14	1	1	1	1		3	7	3	4	1		14	2	1	1	1	
Chemotherapy Phases																			
Induction	1	15	0	1	0	1	0.329	4	6	6	1	1	0.399	15	1	1	0	1	0.383
Consolidation	0	6	0	0	1	0		3	1	1	2	0		6	0	0	1	0	
Reinduction/ intensification	1	2	0	0	0	0		2	1	0	0	0		3	0	0	0	0	
Maintenance	3	18	3	0	0	0		5	11	7	1	0		20	4	0	0	0	
ALL Risk																			
Standard	0	8	0	0	0	0	0.771	1	5	2	0	0	0.494	8	0	0	0	0	0.787
High	5	33	3	1	1	1		13	14	12	4	1		36	5	1	1	1	

Note: BN: Below normal; N: Normal; L: Level; the statistical test used was the chi-square test

As presented in table 3, the results indicated a significant differences between AST levels and the chemotherapy phase ($p<0.05$). However, no significant differences in AST levels were observed based on gender, age or ALL risk ($p>0.05$). In contrast, ALT levels exhibited significant differences in relation to both chemotherapy phase and ALL risk ($p<0.05$), while no such differences were found with respect to gender and age ($p>0.05$).

Fig. 1 illustrated the distribution of AST and ALT levels in patients undergoing chemotherapy across four phases: induction, consolidation, intensification, and maintenance. AST levels had a median of 27 U/l during induction, increased to 40 U/l in consolidation, dropped to 16 U/l in intensification, and stabilized at 22.5 U/l in the maintenance phase. Similarly, ALT levels started with a median of 53.5 U/l in the induction phase, rose to 60 U/l in consolidation, declined significantly to 16 U/l during intensification,

and slightly increased to 17.5 U/l in maintenance. Overall, both AST and ALT levels showed a downward trend throughout the phases, reflecting possible liver adaptation or improvement in liver function during chemotherapy.

Table 3: Differences in the AST and ALT profile of pediatric ALL patients based on the sociodemographic profile

Socio-demographics	AST Level			ALT Level		
	Normal (n)	Abnormal (n)	P-value	Normal (n)	Abnormal (n)	P-value
Gender						
Female	20	5	1.000[b]	18	7	0.768[b]
Male	21	6		18	9	
Age						
Toddler	14	4	0.154[a]	13	5	0.254[a]
Child	15	1		13	3	
Adolescent	12	6		10	8	
Chemotherapy Phase						
Induction	13	5	0.028*[a]	8	10	0.002*[a]
Consolidation	3	4		3	4	
Reinduction/intensification	3	0		3	0	
Maintenance	22	2		22	2	
ALL Risk						
Standard	8	0	0.178[b]	8	0	0.047*[b]
High	33	11		28	16	

Note: *p<0.05 (significant); [a]Chi-Square Test; [b]Fisher's exact test

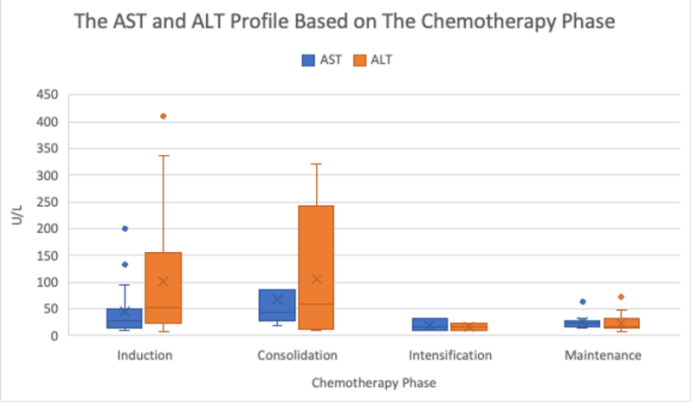

Fig. 1: The AST and ALT profile based on the chemotherapy phase

Table 4 indicated that almost all patients were in a non-hepatotoxic level, comprising about 96.1%, with only two patients displaying signs of hepatotoxicity. The statical analysis also demonstrated no significant differences. Between sociodemographic profile and the occurrence of hepatotoxicity, with p-values (p>0.05) across all categories, including gender, age, chemotherapy phase and ALL ris.

Table 4: The relationship between sociodemographic profile and the incidence of hepatotoxicity

Sociodemographics	Hepatotoxic (n)	Non-hepatotoxic (n)	p-value
Gender			
Female	0	25	0.491[b]
Male	2	25	
Age			
Toddler	0	18	0.140[a]
Child	0	16	
Adolescent	2	18	
Chemotherapy phase			
Induction	1	17	0.350[a]
Consolidation	1	6	
Reinduction/intensification	0	3	
Maintenance	0	24	
ALL risk			
Standard	0	8	1.000[b]
High	2	42	

Note: [a]Chi-Square Test; [b]Fisher's exact test

DISCUSSION

According to table 1, the study included 52 pediatric ALL patients, comprising 25 females (48.1%) and 27 males (51.9%). The data reveals that the number of male patients with ALL is higher than that of females. This finding aligns with Shah's research (2016) and Yildirim's research (2023), which states that ALL is more prevalent

in males than in females [6, 7]. In terms of age distribution, there were 18 patients (34.6%) in the toddler group, 16 patients (30.8%) in the child group, and 18 patients (34.6%) in the adolescent group. This is consistent with Hasni's study (2021), which found that most pediatric ALL patients undergoing chemotherapy fall within the age range of 6-18 y [8].

The treatment of ALL comprises four phases: induction, consolidation, intensification/reinduction, and maintenance. Based on the data collected, the induction phase included 18 patients (34.6%), the consolidation phase had 7 patients (13.5%), intensification/reinduction involved 3 patients (5.8%), and the maintenance phase consisted of 24 patients (46.1%). These findings suggest that the maintenance phase is the most commonly experienced phase and represents the final chemotherapy stage in ALL treatment. Additionally, ALL treatment is categorized into two risk levels: standard and high. Among the patients, 8 (15.4%) were classified as standard risk, while 44 patients (84.6%) were classified as high risk. Therefore, high risk was more prevalent in ALL patients. One of the factors in determining the risk stratification for leukemia is the leukocyte count at the time of diagnosis [9, 10].

The initial treatment for ALL, known as the induction phase and the chemotherapeutic agents commonly used during this phase include prednisone, vincristine, L-asparaginase, daunorubicin, and intrathecal methotrexate. Consolidation, Conducted after remission induction and before long-term maintenance therapy; this phase is also referred to as intensification therapy. Common drugs in consolidation/intensification regimens include high-dose methotrexate, cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, thioguanine, vincristine, corticosteroids, and L-asparaginase/pegaspargase. For high-risk patients, anthracyclines may be added to the regimen. Consolidation therapy generally lasts 1-2 mo and aims to further reduce the number of remaining leukemia cells in the body. The objective of maintenance therapy is to eradicate any residual leukemia cells and achieve sustained clinical remission. Two critical medications in maintenance chemotherapy are oral methotrexate and 6-mercaptopurine [11].

Liver function tests were the primary baseline indicators of liver function and health in patients undergoing anticancer treatments, with elevated liver function tests levels accounting for the majority of therapy-related hepatotoxicity cases. The presence of liver damage or dysfunction necessitated careful adjustment of drug dosages and modifications to the patient's therapeutic regimen [12]. Therefore, it is essential to identify patients at risk of hepatotoxicity prior to starting anticancer therapy and to continuously monitor those undergoing treatment for liver-related complications [13].

Chowdhury's study (2022) reported an increase in bilirubin and ALT levels during induction phase [14]. In a similar finding, Mekonnen (2022) reported that most patients exhibited clinically significant hepatotoxicity. The rise in liver function test values from baseline to post-induction was statistically significant [15]. This observastion is consistent with the findings of our research, which also detected abnormal elevations in ALT and bilirubin levels. However, the average bilirubin levels in our study remained within the normal range (table 2). Furthermore, previous studies highlighted a notable rise in bilirubin levels after induction chemotherapy, attributed to toxic effects of anticancer drugs [16].

Following the administration of high-dose methotrexate, particularly during the consolidation phase, temporary increases in serum aminotransferase levels are commonly observed, though these levels generally normalize without leading to chronic liver damage [17]. The risk of liver damage is heightened with the use of multiple chemotherapy agents [18, 19]. In this study, five hepatotoxic chemotherapy drugs administered during the consolidation phase were associated with more pronounced increases in liver enzyme levels compared to other phases (table 3, fig. 1). High-dose methotrexate is given in combination with leucovorin during this phase. While methotrexate impacts both healthy and cancerous cells, leucovorin mitigates its effects on healthy cells. At standard doses, methotrexate is excreted unchanged via urine; however, at high doses, it undergoes partial conversion in the liver to 7-hydroxymethotrexate [20, 21]. This finding aligns with the study's observation that average bilirubin levels remained within normal limits, likely due to the protective effects of leucovorin, although AST and ALT levels remained high.

Hashmi's study (2019) highlighted an increase in transaminase enzyme levels during the consolidation phase [22]. Similarly, Zawitkowska's research (2019) reported cases of reduced liver function in some pediatric patients during the same phase [23]. These findings were consistent with the present study, which observed elevated transaminase enzyme and bilirubin levels. Across all chemotherapy phases, certain pediatric ALL patients exhibited increases in bilirubin, AST, and ALT levels, aligning with the findings of Altalib (2023). The rise in aminotransferases and bilirubin was likely linked to liver damage caused by the hepatotoxic effects of anticancer medications. The rise in aminotransferases and bilirubin might be attributed to liver damage resulting from the toxicity of the anticancer medications [14]. Regular monitoring of liver function, particularly ALT levels, is anticipated to help mitigate adverse effects like oxidative stress on the liver. This approach is intended to protect patients from complications that could impair their quality of life.

Intense physical activity can result in greater damage to muscle cells compared to moderate physical activity, leading to elevated levels of AST in the bloodstream. This occurs because high quantities of AST are present in muscle cells, liver cells, and heart muscle, while only small amounts are found in other tissues like the kidneys, pancreas, brain, and red blood cells. Consequently, continuous monitoring is needed to assess liver necrosis, particularly through ALT measurement, as ALT is considered a more sensitive indicator of liver disease and hepatotoxicity compared to AST. Additionally, factors such as obesity, genetics, and immune system disorders may contribute to liver disease, resulting in elevated levels of both AST and ALT in the bloodstream [5, 24].

AST is present in all body tissues but is most concentrated in the heart and liver. Following hepatocellular injury, AST levels typically rise rapidly, initially reaching higher concentrations than ALT due to AST's shorter plasma half-life. However, ALT levels surpass AST levels within 24–48 h. In cases of chronic liver damage, ALT levels are generally higher than AST, but as the condition advances, ALT levels often decline, leading to an increased AST-to-ALT ratio, a pattern commonly observed in cirrhosis [25]. Both enzymes are released into the bloodstream in significant amounts when liver cell membranes are compromised. ALT, being predominantly localized in liver tissue and within the cytosol of hepatocytes, serves as a more specific marker for liver damage compared to AST. Additionally, bilirubin, a byproduct of red blood cell breakdown, is processed by the liver and excreted through feces. Consequently, indications of liver damage can be detected through symptoms like jaundice or elevated bilirubin levels [26].

The ALT levels significantly increased in patients who received blood transfusions. In contrast, patients who did not receive blood transfusions did not show a significant increase in ALT levels. The increased ALT levels in transfused patients could be linked to prior bleeding before the blood donation, which might indicate hepatotoxicity. Hepatotoxicity was found to have a significant correlation with obesity. Among the patients, 15% experienced hepatotoxicity due to chemotherapy, while 5% had mild liver damage [27]. Additionally, drug-induced liver damage occurs more frequently in high-risk patients than in those with standard risk (table 4). Furthermore, liver damage also increased with the number of chemotherapy drugs administered to the patient [18].

Several medications known to cause hepatotoxicity in ALL include methotrexate, 6-mercaptopurine, asparaginase, cytarabine, cyclophosphamide, doxorubicin, daunorubicin, and vincristine [28, 29]. These chemotherapy drugs led to various side effects, especially when used at high doses or in combination [18, 30]. Among these, methotrexate, 6-mercaptopurine, and asparaginase are particularly likely to induce hepatotoxicity compared to cyclophosphamide, cytarabine, and doxorubicin [28]. Drugs such as methotrexate, 6-mercaptopurine, asparaginase, vincristine, cytarabine, and steroids have varying degrees of hepatotoxicity. When given in high doses, these cytotoxic drugs can result in elevated transaminase levels and

increased serum bilirubin concentrations, as they impair the liver's metabolic function [31]. A study in Japan involving pediatric ALL patients showed a threefold increase in ALT levels, which normalized after chemotherapy, while bilirubin levels remained within the normal range throughout the treatment [32]. According to the study by Bhutadiya (2021), no cancer therapy is free from side effects. Additionally, complications in cellular targeting and second cancers caused by therapy have also been observed. Moving forward, scientists continue to search for new and effective modes of cancer treatment to ensure fewer or even no side effects with a promising survival rate [33].

Hepatotoxicity presented in diverse forms, ranging from acute and transient increases in liver function tests, such as bilirubin and liver enzymes, to long-term complications, including cirrhosis or liver failure, if left undetected [34]. The primary approach to managing chemotherapy-induced hepatotoxicity includes evaluating the reduction of the suspected hepatotoxic drug's dose or stopping the chemotherapy drug responsible for the liver damage if it continues despite dose adjustment [35, 36]. In countries like India, where treatment facilities are limited, pure accelerated radiation therapy with brachytherapy, without the use of concurrent chemotherapy, may be a viable and equally effective option for elderly patients, those who decline treatment, individuals with contraindications to chemotherapy, or those with comorbid conditions. However, brachytherapy is not suitable for treating cancers that have metastasized or ALL [37].

The study has several strengths. It focused specially on pediatric ALL patients undergoing chemotherapy. The comprehensive data collection, which includes sociodemographic data (gender, age, chemotherapy phase, and ALL risk level) and clinical data (bilirubin, AST, and ALT), allows for an in-depth analysis of the factors influencing liver function during chemotherapy. However, the study also had limitations. A small sample size, such as the 52 pediatric patients included in this study, can limit statistical power, reducing the ability to detect small but potentially meaningful differences between groups. Furthermore, conducting the study at a single hospital limits the external validity or generalizability of the findings. The results may not be applicable to other healthcare settings, regions, or diverse patient populations, potentially reducing the broader relevance of the conclusions. The retrospective nature limited the ability to establish causal relationships, and the lack of longitudinal data prevented tracking long-term effects of chemotherapy on liver function. By addressing these limitations, future research could strengthen its findings and provide more robust insights applicable to a wider population.

CONCLUSION

This study revealed that liver function tests (AST and ALT) were influenced by chemotherapy phases and ALL risk levels in pediatric patients undergoing treatment for ALL). Meanwhile, no significant differences were observed in the bilirubin profile based on sociodemographic profile. Significant differences in AST levels were associated with chemotherapy phases, while ALT levels were significantly influenced by both chemotherapy phases and ALL risk levels. However, no associations were identified between sociodemographic factors (gender, age) and liver function tests or hepatotoxicity. Hepatotoxicity was rare, affecting only 3.9% of patients. These findings highlight the importance of routine monitoring of liver function, particularly ALT and AST, to prevent and manage chemotherapy-induced liver damage in pediatric ALL patients.

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AUTHORS CONTRIBUTIONS

RY: Principal Investigator, Conceptualization, Supervision, Writing-Original Draft; DP: Supervision, Review and Editing; and NA: Data Collection, Writing-Original Draft. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

There is no conflict of interest from all the authors.

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