Asian Journal of Pediatric Research

Volume 14, Issue 8, Page 48-56, 2024; Article no.AJPR.121353
ISSN: 2582-2950

A Single-center Clinical Analysis of Drug-Induced Liver Injury in Children with Acute Leukemia

Bai Taomin [a], Liu Hong [a*], Liu Na [a], Niu Qian [a] and Jiao Fuyong [a]

[a] Children's Hospital of Shaanxi Provincial People's Hospital, Shaanxi Provincial Pediatric Diagnosis and Treatment Center, Xi'an-710068, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i8380

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/121353

Original Research Article

Received: 10/06/2024
Accepted: 12/08/2024
Published: 16/08/2024

ABSTRACT

Introduction: To analyze the clinical characteristics and influencing factors of drug-induced liver injury (DILI) in pediatric patients with newly diagnosed Acute Lymphoblastic Leukemia (ALL) during chemotherapy, using a retrospective analysis.
Methods: A retrospective analysis was conducted on 189 pediatric ALL patients treated at our institution from January 2019 to March 2024. The incidence and related factors of DILI were assessed, including body mass index (BMI), vitamin D levels, absolute neutrophil counts, and the number of blood transfusions.
Results: The study found that the incidence of DILI was 21.34%. Statistical analysis indicated that BMI, vitamin D levels, absolute neutrophil counts, and the number of transfusions were independent factors influencing the occurrence of DILI during chemotherapy in children with ALL

**Corresponding author: Email: 3105089948@qq.com;*

Cite as: *Taomin, Bai, Liu Hong, Liu Na, Niu Qian, and Jiao Fuyong. 2024. "A Single-Center Clinical Analysis of Drug-Induced Liver Injury in Children With Acute Leukemia". Asian Journal of Pediatric Research 14 (8):48-56. https://doi.org/10.9734/ajpr/2024/v14i8380.*

(P<0.05). Moreover, DILI presented in various forms, predominantly as hepatocellular injury, mixed type, and cholestatic type, with hepatocellular injury being the most common.
Conclusion: Body mass index, vitamin D levels, absolute neutrophil counts, and the number of transfusions are critical independent factors affecting the development of drug-induced liver injury in pediatric patients with acute leukemia during chemotherapy. In clinical practice, proactive intervention on these factors is essential. Prompt actions such as discontinuing or adjusting medication dosages, hepatic protection, enzyme reduction, and jaundice management are vital to ensure the recovery of all patients.

Keywords: Children; acute lymphoblastic leukemia; chemotherapy; drug-induced liver injury.

1. INTRODUCTION

Acute leukemia is one of the most common malignancies in children, and chemotherapy is the primary treatment modality. However, the use of chemotherapeutic drugs can lead to various side effects, with liver damage being a common complication. A study conducted in Ethiopia observed hepatotoxicity in 15% of patients, with mild liver damage in 5% of cases [1]. Another study in Azerbaijan focused on toxic liver injury during supportive care in children with acute leukemia, finding toxic hepatitis in 82% of patients, with 23.5% having mild, 50.9% moderate, and 7.8% severe hepatitis [1]. Genetic association studies involving children, adolescents, and young adults treated for acute leukemia identified variants in UGT1A1 and PNPLA3 related to hepatotoxic effects. The UGT1A1 variant was found to be a major driver of increased bilirubin levels, while other genetic variations led to elevated transaminase levels [2]. Finally, an Iranian study evaluated hepatic complications in pediatric patients with hematological malignancies receiving high-dose methotrexate treatment [3]. They found that in a certain proportion of cases, liver enzyme levels were elevated, and some patients had liver and spleen enlargement as well as fatty liver [4].

In addition to these studies, our research is part of a key project titled "Chinese Medicine Patching Therapy for Pediatric Tic Disorder: 'Belt and Road' Collaborative Research," funded by the Shaanxi Provincial Key R&D Program (Project Number: 2023-GHZD-41). This project, led by Shaanxi Provincial People's Hospital under the direction of Dr. Niu Qian, aims to investigate the efficacy and mechanisms of Chinese medicine patching therapy for pediatric tic disorders through international collaboration under the "Belt and Road" initiative. The project duration is from January 1, 2023, to December 31, 2024.

Currently, research on drug-induced liver injury in children undergoing chemotherapy for acute leukemia is insufficient, lacking systematic clinical data and in-depth mechanistic studies. This results in the absence of unified guidelines for the prevention and treatment of such liver injuries in clinical practice. This paper aims to analyze the clinical characteristics and risk factors of drug-induced liver injury in children with acute leukemia undergoing chemotherapy, providing guidance for prevention and treatment. This will offer clinicians more scientific and effective treatment recommendations to reduce chemotherapy-induced liver dysfunction and improve the safety and efficacy of chemotherapy.

2. MATERIALS AND METHODS

2.1 Study Design and Patient Selection

A retrospective study design was used to track changes in liver function in children with acute leukemia undergoing chemotherapy to evaluate the impact of chemotherapeutic drugs on the liver. The following are the patient selection criteria.

2.1.1 Inclusion criteria

(1) Diagnosed with acute leukemia.
(2) Aged between 1 to 18 years.
(3) Receiving standardized chemotherapy.

2.1.2 Exclusion criteria

(1) Severe comorbidities such as significant heart, kidney, or other vital organ dysfunction.
(2) Pre-existing significant liver function abnormalities or chronic liver disease.
(3) History of liver surgery or transplantation.
(4) Kown allergy to chemotherapy drugs [5].

2.2 Data Collection and Processing

Treatment data from 189 pediatric leukemia patients treated at our hospital from January

2019 to March 2024 were retrospectively analyzed. The cohort included 114 males and 75 females, aged between 2 and 18 years, with an average age of 12.1 years. Patients were divided into two groups based on liver damage occurrence: 149 patients without liver damage (control group) and 40 patients with DILI (observation group).

Data collected included six blood indicators: albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), direct bilirubin, total bilirubin, and prealbumin.

Additionally, data on patients' BMI, vitamin D levels, absolute neutrophil counts, and the number of blood transfusions were also collected.

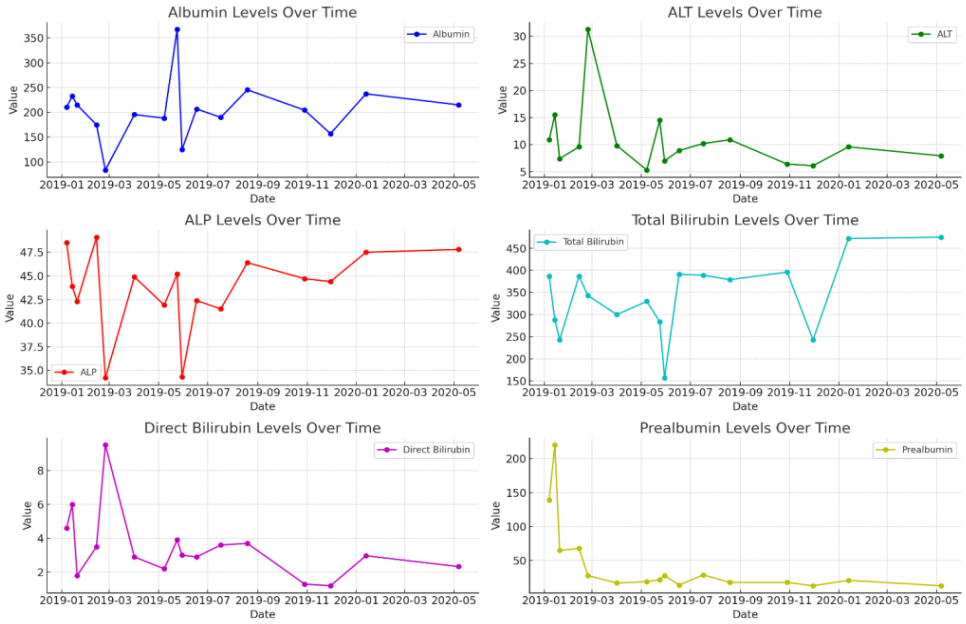

Fig. 1. Data sequence chart of six indicators for patient "Bai **" [ALT] Alanine Aminotransferase; [ALP] Alkaline Phosphatase

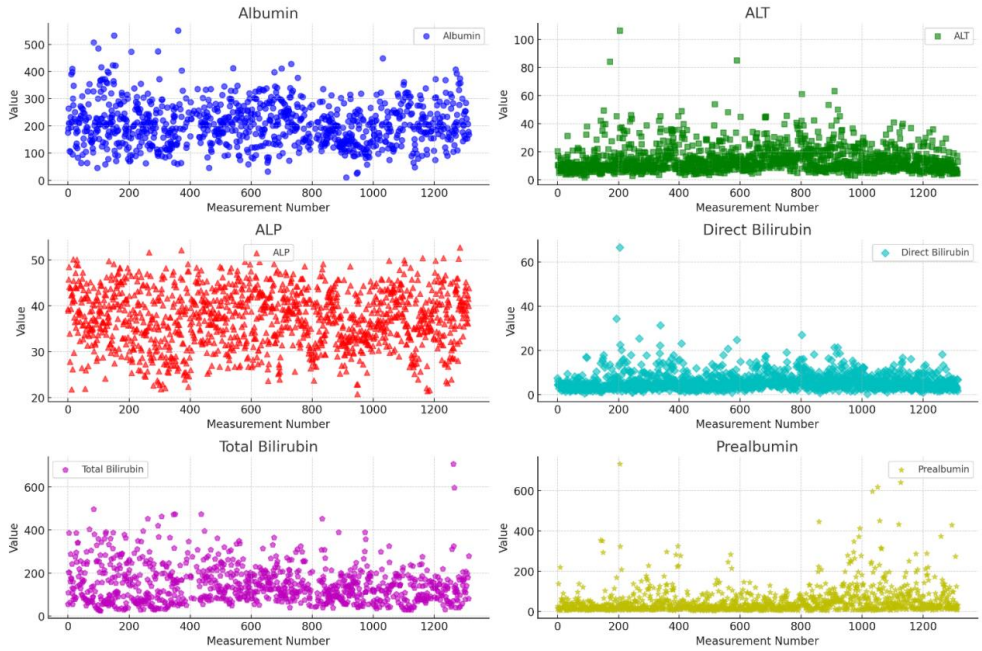

Fig. 2. Time series of all data (including six indicators: Albumin, ALT, ALP, Total Bilirubin, Direct Bilirubin, Prealbumin). [ALT] Alanine Aminotransferase; [ALP] Alkaline Phosphatase

2.3 Liver Function Testing and Evaluation of Drug-induced Liver Injury

Liver function tests are crucial for assessing liver health, diagnosing, and monitoring drug-induced liver injury (DILI) [6]. Common liver function indicators include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL). ALT and AST are enzymes present in liver cells that are released into the bloodstream when liver cells are damaged, leading to elevated serum levels [7]. ALT is primarily found in the liver, and its elevated levels typically indicate hepatocellular damage. AST is widely present in various tissues, including the liver, heart muscle, and skeletal muscle, so elevated AST levels can reflect damage to multiple tissues. ALP is mainly found in liver bile duct cells, and its elevated levels may be associated with cholestasis [8]. TBIL is the total bilirubin in the blood, including direct bilirubin (DBIL) and indirect bilirubin (IDBIL). Elevated TBIL levels usually indicate impaired bilirubin excretion by the liver [9].

Albumin is the main plasma protein synthesized by the liver. In liver function assessment, albumin levels reflect the synthetic function of the liver. Albumin has a relatively long half-life (about 20 days), so its response to liver damage is slow and is not suitable for assessing acute liver injury. Prealbumin is also a plasma protein synthesized by the liver, but it has a shorter half-life (about 2 days), making it more responsive to changes in liver synthetic function. Clinically, prealbumin levels are often measured to assess acute liver injury and nutritional status. A decrease in prealbumin usually indicates malnutrition or decreased liver function earlier than albumin. Changes in prealbumin levels are very useful for judging the prognosis of liver disease patients and monitoring treatment effects.

In the evaluation of DILI, the patterns of changes in these indicators help determine the type and extent of liver damage [10]. For example, significant elevations in ALT and AST may indicate hepatocellular damage, while elevations in ALP and TBIL may suggest cholestasis or mixed-type liver damage. Additionally, the R-value (ALT/AST ratio) is used to distinguish between hepatocellular and cholestatic liver damage.

When evaluating DILI, it is also necessary to consider the patient's clinical manifestations, other potential causes of liver damage, and detailed information about drug exposure. Integrating this information allows for a more accurate diagnosis and assessment of drug-induced liver injury, providing appropriate treatment and management strategies for the patient.

2.4 Statistical Analysis Methods

In this study, logistic regression can be used to assess the relationship between different factors (such as gender, age, BMI, vitamin D levels, absolute neutrophil counts, and the number of blood transfusions) and the occurrence of drug-induced liver injury. By constructing a logistic regression model, we can calculate the impact of each factor on the probability of drug-induced liver injury, thereby determining which factors are independent influencing factors of drug-induced liver injury.

3. RESULTS

3.1 Incidence and Clinical Manifestations of Drug-induced Liver Injury

The incidence of DILI among pediatric acute leukemia patients undergoing chemotherapy was found to be 21.34%. The types of liver damage were categorized as follows:

1. Hepatocellular injury type: 17.19%, where ALT levels exceeded twice the upper normal limit (normal range 0–40 U/L).
2. Cholestatic type: 3.48%, where ALP levels exceeded twice the upper normal limit (normal range 40–160 U/L).
3. Mixed type: 0.67%, where both ALT and ALP levels exceeded twice the upper normal limit, with an R-value (ALT/AST ratio) between 2 and 5.

The correlation analysis of the six blood indicators, with the results of the correlation matrix, is as follows:

It can be observed that:

1. There is a very high correlation (0.89) between total bilirubin and direct bilirubin, which is expected as they both participate in bile formation and metabolism.
2. The correlation among other indicators is weaker.

Based on statistical analysis, the clinical manifestations of DILI during chemotherapy for pediatric acute leukemia are as follows:

The clinical manifestations of drug-induced liver injury include fatigue (25 cases), nausea and anorexia (20 cases), abdominal pain (5 cases), diarrhea (7 cases), liver enlargement (31 cases), and jaundice (9 cases).

These clinical manifestations may vary due to individual differences. During treatment, physicians will closely monitor patients' liver function to promptly detect and manage drug-induced liver injury.

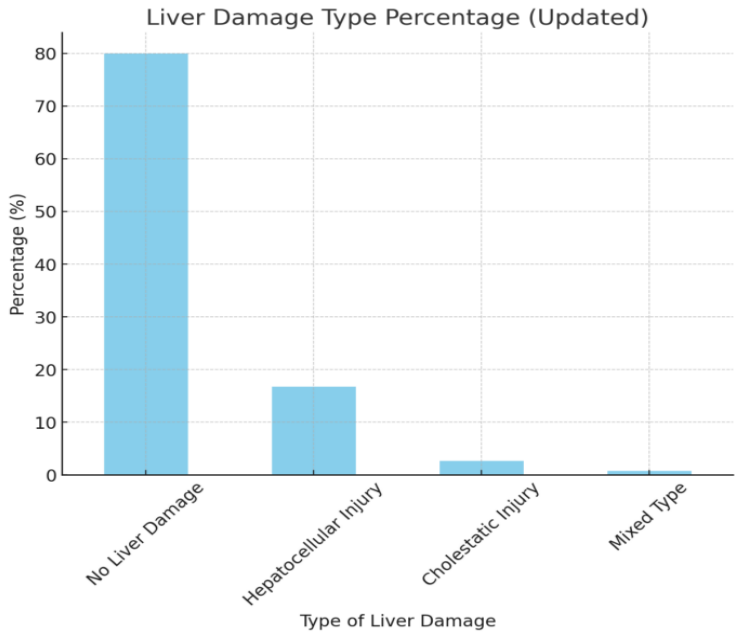

Fig. 3. Percentage of Types of Liver Damage

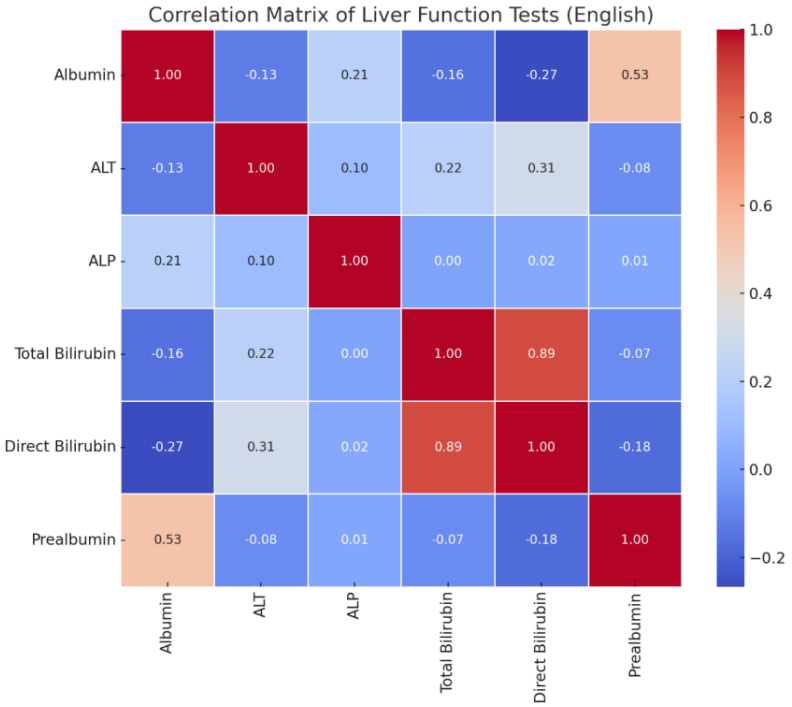

Fig. 4. Correlation matrix of six blood indicators [ALT] Alanine Aminotransferase; [ALP] Alkaline Phosphatase

Table 1. Analysis of factors related to drug-induced liver injury during chemotherapy for pediatric acute leukemia

Factors	Control Group (n=149)	Observation Group (n=40)	χ^2 Value	P Value
Gender	Male: 94 (63.09%) Female: 55 (36.91%)	Male: 18 (45.00%) Female: 22 (55.00%)	0.539	0.305
Age	2~: 58 (38.93%) 6~: 54 (36.24%) 9~: 37 (24.83%)	2~: 13 (32.50%) 6~: 6 (15.00%) 9~: 21 (52.50%)	0.542	0.524
BMI	<18.5: 65 (43.62%) 18.5~24: 53 (35.57%) >24: 31 (20.81%)	<18.5: 11 (27.50%) 18.5~24: 22 (55.00%) >24: 7 (17.50%)	23.211	0.007
Vitamin D Levels	Normal: 123 (82.55%) Reduced: 26 (17.45%)	Normal: 21 (52.50%) Reduced: 19 (47.50%)	9.501	0.000
Absolute Neutrophil Counts	Normal: 109 (73.15%) Deficient: 40 (26.85%)	Normal: 16 (40.00%) Deficient: 24 (60.00%)	10.458	0.001
Number of Blood Transfusions	Yes: 84 (56.38%) v: 65 (43.62%)	Yes: 13 (32.50%) No: 27 (67.50%)	6.882	0.027

Note: [BMI] Body Mass Index

3.2 Analysis of Related Factors

Multiple factors significantly increased the risk of liver damage, including BMI, vitamin D levels, absolute neutrophil counts, and the number of blood transfusions ($P<0.05$),as shown in Table 1. These findings suggest that thorough assessment and active management of these risk factors are crucial when treating pediatric acute leukemia patients to reduce the probability of drug-induced liver damage.

4. DISCUSSION

In this study, the incidence of drug-induced liver injury (DILI) during chemotherapy for pediatric acute leukemia was 21.34%, which is consistent with the range observed in other studies. For instance, Wang Juping et al [11]. reported a similar incidence. The clinical manifestations of DILI are diverse, primarily including fatigue, nausea, anorexia, abdominal pain, diarrhea, fever, liver enlargement, and jaundice, typically occurring within 2 to 21 days after drug administration.

This study further analyzed the independent influencing factors of DILI and found that BMI, vitamin D levels, absolute neutrophil counts, and the number of blood transfusions were significantly associated with the occurrence of liver injury. These results highlight the importance of comprehensive risk assessment before chemotherapy to take appropriate preventive measures, adjust chemotherapy regimens, or modify drug dosages, especially in patients with other risk factors.

The BMI is a commonly used standard for assessing body fat [12]. Generally, a BMI between 18.5 and 24 kg/m² is considered normal, while a BMI over 24 kg/m² is categorized as overweight or obese. This study shows that obese pediatric acute leukemia patients have a significantly higher incidence of drug-induced liver injury compared to patients with normal weight. This may be due to enhanced lipid metabolism in the liver of obese patients, affecting drug metabolism, leading to drug accumulation and subsequent liver damage.

Vitamin D is a fat-soluble vitamin stored in the body's fat tissue. In obese individuals, more vitamin D may be stored in the abundant fat tissue [13], reducing its levels in the blood. Vitamin D can be synthesized in the skin with the help of sunlight. Studies have shown that the skin of obese individuals may be less effective in synthesizing vitamin D due to a non-linear relationship between skin surface area and body weight or reduced outdoor activities leading to less sunlight exposure [14]. Obesity is associated with metabolic changes that may affect vitamin D metabolism and activation, and inflammation related to obesity may interfere with vitamin D metabolism and function. Thus, vitamin D levels are an independent factor for drug-induced liver injury.

Low absolute neutrophil counts and patients receiving transfusions in a bone marrow-suppressed state have an increased risk of infection, requiring extensive antibiotic use, a common cause of drug-induced liver injury [15]. Infections can release large amounts of inflammatory factors affecting liver cells [16]. Additionally, infections may activate the immune mechanisms of patients, causing immune damage to liver cells and exacerbating liver injury.

This study underscores the importance of comprehensive risk assessment before chemotherapy, especially for patients with other health issues [17]. Chemotherapy drug selection and dosage adjustments should consider these independent risk factors to mitigate potential liver damage. Real-time liver function monitoring and proactive preventive measures, such as appropriate use of hepatoprotective drugs and infection control, are crucial to prevent DILI development.

In terms of treatment strategies, once DILI occurs, timely discontinuation or adjustment of medication dosages, combined with the use of hepatoprotective, enzyme-reducing, and jaundice-relieving drugs, can lead to effective recovery in most patients. These treatment measures have proven to significantly improve patient outcomes in practice [18]. Additionally, regular liver function tests and clinical monitoring are essential to detect any potential liver damage promptly and respond quickly.

Despite the important insights provided by this study into the safety of chemotherapy in pediatric acute leukemia patients, we also acknowledge some limitations, such as the limited sample size and the lack of long-term health impact tracking. Future research should focus on larger and more diverse populations, conduct multi-center and long-term follow-up studies to more comprehensively understand the pathogenesis and long-term effects of DILI, and optimize prevention and treatment strategies.

5. CONCLUSION

In this study, we analyzed the clinical characteristics and influencing factors of drug-induced liver injury (DILI) in pediatric patients with newly diagnosed acute lymphoblastic leukemia (ALL) undergoing chemotherapy. Our findings reveal that the incidence of DILI in this patient population is 21.34%. The most common type of liver injury observed was hepatocellular, followed by cholestatic and mixed types. Key independent factors influencing the occurrence of DILI included body mass index (BMI), vitamin D levels, absolute neutrophil counts, and the number of blood transfusions.

The clinical manifestations of DILI varied among patients, with symptoms ranging from fatigue and nausea to liver enlargement and jaundice. Our analysis underscores the importance of thorough pre-treatment assessments and the proactive management of risk factors to minimize the likelihood of liver injury during chemotherapy.

Based on our study, clinicians should consider adjusting chemotherapy regimens and dosages, especially in patients identified with higher risk factors such as obesity, vitamin D deficiency, low neutrophil counts, and those requiring frequent blood transfusions. Regular liver function monitoring and the use of hepatoprotective strategies are essential to ensure patient safety and improve treatment outcomes.

Future research should focus on larger and more diverse patient cohorts to further validate these findings and develop comprehensive guidelines for the prevention and management of DILI in pediatric leukemia patients. Additionally, long-term follow-up studies are needed to understand the chronic impacts of chemotherapy-induced liver injury and to optimize treatment protocols accordingly.

By implementing these measures, we aim to enhance the efficacy and safety of chemotherapy for pediatric patients with acute leukemia, ultimately improving their overall prognosis and quality of life.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, patient(s) written consent and parental consent has been collected and preserved by the author(s).

ETHICS APPROVAL

This study was approved by the Medical Ethics Committee of Shaanxi Provincial People's

Hospital (Approval Number: 2023-GHZD-41) on September 25, 2023. The principal investigator is Niu Qian, along with researchers Jiao Wenyan, Tungalag Osgonbatar, Jiao Fuyong, et al.

The study was reviewed and approved by the Ethics Committee through a meeting review process.

The Ethics Committee determined that the study met the required ethical guidelines for research involving human participants and granted approval. The committee contact person is Wu Min, reachable at 029-85251331-2610, with the address at No. 256 Youyi West Road, Xi'an, Shaanxi, postal code 710068.

ACKNOWLEDGEMENTS

The authors like to thank all study participants and other individuals involved in any process of this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ayal Tsegaye Mekonnen, Temesgen Gebeyehu Wondmeneh. Evaluation of liver function tests to identify hepatotoxicity among acute lymphoblastic leukemia patients who are receiving chemotherapy induction. Dental Science Reports; 2022.
DOI: 10.1038/s41598-022-17618-w
2. Mireldar Babayev, A. Afaq. The course of toxic hepatitis in leukemic patients at the stage of support therapy. Hematology Transfusion and Cell Therapy;2022.
DOI: 10.1016/j.htct.2022.09.1264
3. Yang W, Karol SE, Hoshitsuki K, et al. Association of inherited genetic factors with drug-induced hepatic damage among children with acute Lymphoblastic Leukemia. JAMA Netw Open. 2022;5(12): e2248803.
DOI:10.1001/jamanetworkopen.2022.48803.
4. Maryam Shoaran, Azim Rezamand, Soheyla Ghari, Leila Vahedi. Evaluation of hepatic complications for high dose methotrexate in children: 10 years after treatment of malignancy. International Journal of Pediatrics; 2021.
DOI: 10.22038/IJP.2020.54376.4301
5. Meftahul Jannat, Akm Amirul Morshed, Sayeeda Anwer, Shahnoor Islam. Effect of chemotherapy on liver function during induction of remission in children with acute lymphoblastic leukemia receiving standard protocol. Journal of Dhaka Medical College; 2021.
DOI: 10.3329/JDMC.V29I1.51168
6. M. Skrypnyk, G. Maslova, T. Lymanets, R. I. Skrypnyk. The overweight and obesity role in the occurrence of chemotherapy-induced hepatotoxic reactions in patients with acute myeloid leukemia. Wiadomości Lekarskie; 2022.
DOI: 10.36740/wlek202206114
7. Horváth Adrienne, Papp Zsuzsanna Erzsébet. Chemotherapy Induced Liver Toxicity in Children with Malignant Diseases; 2018.
DOI: 10.2478/ORVTUDERT-2018-0002
8. Sayla Chowdhury, Afiqul Islam, Mahbuba Sultana, Mir Iftekhar Mostafiz. Assessment of Renal and Liver Function Tests Before and After Induction of Chemotherapy in Newly Diagnosed Acute Lymphoblastic Leukemia in Children. Community Based Medical Journal; 2022.
DOI: 10.3329/cbmj.v11i1.60264
9. Emilia Urrutia-Maldonado, Ana Abril-Molina, María Alés-Palmer, Jose María Gómez-Luque, Paloma Rueda, Esther Ocete-Hita. Chemotherapy-induced liver injury in children. Anales De Pediatria; 2019.
DOI: 10.1016/J.ANPEDE.2019.08.001
10. Liu J, Zhang X, Li Y, Wang Q, Yang H, Chen S, Zhang Y. A Risk scoring model for high-dose methotrexate-induced liver injury in children with acute lymphoblastic leukemia based on gene polymorphism study. Frontiers in Pharmacology. 2023;14: 819589.
Available:https://doi.org/10.3389/fphar.2022.819589
11. Wang Juping, Li Xiaoqin, Li Yongchun. Clinical analysis of drug-induced liver injury during chemotherapy for pediatric acute leukemia. Journal of Jinzhou Medical University. 2020;41(02):32-35.
DOI: 10.13847/j.cnki.lnmu.2020.02.009.
12. Jiao Yanguang. Efficacy of reduced glutathione combined with polyene phosphatidylcholine in the treatment of acute drug-induced liver injury. Practical Clinical Medicine of Integrated Traditional Chinese and Western Medicine.2024;24 (01):20-23.
DOI:10.13638/j.issn.1671-4040.2024.01.006

13. Wang Limin, Yan Jianguo, Gan Yu, et al. Analysis of complications and prognosis of different clinical types of drug-induced liver injury in children. Chinese Journal of Hepatology (Electronic Edition), 2022;14(04):62-67.
14. Tong Jili, Wang Liping. Diagnostic value of 25-hydroxyvitamin d3 combined with immunoglobulin level detection in childhood obesity and the interventional effect of Vitamin D. Maternal and Child Health Care of China. 2024;39(08):1366-1369.
DOI:10.19829/j.zgfybj.issn.1001-4411 2024.08.003
15. Di Paola F, Molleston JP. Drug-induced liver injury in children. Curr Hepatology Rep. 2018;17:283–291.
Available:https://doi.org/10.1007/s11901-018-0413-y
16. Zhang Ying, Xu Hongmei. Clinical cases and etiological discussion of liver damage in children with adenovirus infection. Journal of Clinical Pediatrics. 2024;42(03): 259-263+276.
17. Monge-Urrea F, Montijo-Barrios E. Drug-induced liver injury (DILI) is a rare, underdiagnosed cause of liver disease in children. Journal of Pediatric Gastroenterology and Nutrition. 2022;75(4): 391-395.
Available:https://doi.org/10.1097/MPG.0000000000003535
18. Monge-Urrea F, Montijo-Barrios E. Drug-induced liver injury in pediatrics. J Pediatr Gastroenterol Nutr. 2022;75(4):391-395.
DOI:10.1097/MPG.0000000000003535
Epub 2022 Jun 21. PMID: 35727646.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/121353