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Original Article

Liver Involvement in Childhood Cancers: Clinical and Laboratory Insights

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A B S T R A C T

Introduction: Liver involvement is observed in various malignancies and is characterized by abnormal liver function tests, imaging findings, or clinical signs linked to the liver. This study aimed to evaluate hepatic manifestations in childhood malignancies.

Materials and Methods: This cross-sectional descriptive study analyzed hepatic manifestations in children under 18 with malignancy admitted to the pediatric oncology ward between April 2016 and April 2020.

Results: Among the 130 patients studied, 82 (63%) were male, and 48 (37%) were female. The mean age was 5.9 ± 4.31 years. Patients with hepatoblastoma, lymphoma, and leukemia exhibited the highest rates of abnormal liver enzyme levels. Elevated aspartate aminotransferase levels were most frequently noted in patients with hepatoblastoma (83.3%), non-Hodgkin's lymphoma (58.3%), and acute lymphoblastic leukemia (32.7%). Similarly, elevated alanine aminotransferase levels were highest in patients with hepatoblastoma (50%), Hodgkin's lymphoma (16.7%), and acute myeloblastic leukemia (22.2%). Hepatomegaly was the most common liver-related clinical sign, occurring in 41.5% of patients.

Conclusion: The findings indicate that clinical and laboratory liver involvement is highly prevalent among children with malignancies. Such involvement can provide insights into disease progression and play a critical role in treatment planning.

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Introduction

Despite increased incidence rates, childhood malignancies remain rare, accounting for less than 1% of all cancer cases in children under 15 in industrialized countries [1, 2]. In Iran, the incidence of childhood malignancies varies geographically, with reported rates ranging from 16.8 per 100,000 for boys and 16.56 per 100,000 for girls [3]. Acute lymphoblastic leukemia (ALL) is the most frequent malignancy and the leading cause of cancer-related deaths in individuals under 20. Leukemic infiltration of organs such as the liver, spleen, mediastinum, and lymph nodes is common at diagnosis [4-6].

Hepatic involvement is a prevalent extranodal manifestation in hematologic and lympho-proliferative malignancies, such as Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and leukemias. Although imaging findings are often nonspecific, they can support diagnostic and therapeutic decisions when combined with clinical and laboratory data [7-9]. Rarely, acute liver failure may occur as an initial manifestation due to malignant cell infiltration, carrying a high mortality risk [10, 11]. In children with acute leukemia, hepatic involvement typically presents as mild hepatomegaly or modest elevations in liver enzymes, while severe hepatic dysfunction at initial presentation is rare [12-14]. Liver infiltration, hepatomegaly, extrahepatic biliary obstruction, and acute hepatic failure also occur in lymphoid neoplasms and have been reported more frequently in NHL than in HL [15]. Obstructive jaundice due to malignancy is also uncommon [16].

Given the diagnostic challenges posed by abnormalities in liver function tests or imaging studies, this study aimed to assess hepatic findings in childhood malignancies.

Materials and Methods

This cross-sectional descriptive study analyzed the clinical and laboratory liver manifestations of children under 18 years with malignancy admitted to the pediatric oncology ward at Ali Ebne Abitaleb Hospital in Zahedan between April 2016 and April 2020. Data, including age, sex, type of malignancy, and clinical findings (e.g., jaundice, hepatomegaly), as well as laboratory findings [(e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP)], were extracted from patient records. Our center uses enzymatic assay and spectrophotometric methods to measure liver enzymes and bilirubin.

Statistical analysis

Data were analyzed using SPSS version 20, with continuous variables expressed as mean ± standard deviation and categorical variables as frequency and percentage. A p-value < 0.05 was considered statistically significant.

Results

One hundred thirty children with malignancy were included, comprising 82 males (63%) and 48 females (37%). The mean age was 5.9 ± 4.31 years. Most patients (79.2%) were under ten years old. ALL was the most common malignancy, accounting for 42.3% of cases.

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Overall, the frequency of clinical findings of liver involvement was higher in children under ten years old. The frequency of malignancies is shown in Table 1. Hepatomegaly (41.5%) was the most frequent liver-related clinical sign, followed by splenomegaly (37%) and abdominal distension (30%). At diagnosis, jaundice was observed in 33.3%, 16.7%, and 8.3% of patients with hepatoblastoma, HL, and neuroblastoma, respectively. There were no cases of pruritus and discoloration of urine and feces in patients. The frequency of different clinical liver findings by type of malignancy is shown in Table 2.

The mean serum level of liver enzymes in hepatoblastoma was higher than other malignancies. The mean serum levels of AST, ALT, and ALP in patients with hepatoblastoma were 127±70 IU/l, 194±169 IU/l, and 1270 ±978 IU/l, respectively. The frequency of abnormal laboratory liver findings by type of malignancy is shown in Table 3. None of the brain tumor patients had abnormal levels of liver enzymes, alkaline phosphatase, and bilirubin.

The highest frequency of ALP levels was also seen in patients with hepatoblastoma. Abnormal bilirubin levels were observed in 50% of patients with hepatoblastoma and 16.7% of patients with NHL and neuroblastoma.

Table 1. Frequency of malignancies in studied patients

Malignancy	No.	Percent
Acute lymphoblastic leukemia	55	42.3
Acute myeloid leukemia	9	6.9
Hodgkin lymphoma	6	4.6
Non hodgkin lymphoma	12	9.2
Neuroblastoma	12	9.2
Hepatoblastoma	6	4.6
Others	30	23.2
Total	130	100

Table 2. Frequency of clinical liver findings by type of malignancy

Malignancy	ALL N=55	AML N=9	HL N=6	NHL N=12	Neuroblastoma N=12	Hepatoblastoma N=6	Others N=30	Total N=130
Abdominal distension	16 (29.1)	4 (44.4)	0 (0)	6 (50)	4 (33.3)	5 (83.3)	4 (13.3)	39 (30)
Ascites	1 (1.8)	0 (0)	0 (0)	2 (16.7)	0 (0)	2 (33.3)	0 (0)	5 (3)
Hepatomegaly	34 (61.8)	6 (66.7)	1 (16.7)	3 (25)	3 (25)	5 (83.3)	2 (6.6)	54 (41.5)
Splenomegaly	33 (60)	5 (55.6)	2 (33.3)	2 (16.7)	2 (16.7)	1 (16.7)	3 (10)	48 (37)
Abdominal pain	11 (20)	2 (22.2)	2 (33.3)	10 (83.3)	5 (41.7)	5 (83.3)	5 (16.6)	30 (23)
Nausea& vomiting	8 (14.5)	0 (0)	0 (0)	1 (8.3)	2 (16.7)	3 (50)	4 (13.3)	18 (14)

ALL=Acute lymphoblastic leukemia; AML= Acute myeloid leukemia; HL= Hodgkin lymphoma; NHL= Non hodgkin lymphoma. Data are presented as No. (%).

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Table 3. Frequency of abnormal laboratory liver findings by type of malignancy

Malignancy	Total	Aspartate aminotransferase	Alanine aminotransferase	Alkaline phosphatase	Total Bilirubin	Direct Bilirubin
Acute lymphoblastic leukemia	55 (100)	18 (32.7)	9 (16.4)	0 (0)	6 (11)	3 (5)
Acute myeloid leukemia	9 (100)	2 (22.2)	2 (22.2)	0 (0)	1 (11)	1 (11)
Hodgkin lymphoma	6 (100)	1 (16.7)	1 (16.7)	0 (0)	0 (0)	0 (0)
Non hodgkin lymphoma	12 (100)	7 (58.3)	1 (8.3)	2 (16.7)	2 (16.7)	2 (16.7)
Neuroblastoma	12 (100)	6 (50)	1 (8.3)	0 (0)	2 (16.7)	1 (8)
Hepatoblastoma	6 (100)	5 (83.3)	3 (50)	1 (16.7)	3 (50)	3 (50)
Others	30 (100)	4 (23.5)	2 (11.7)	1 (5.9)	2 (6)	1 (3)

Data are presented as No. (%).

Discussion

In the present study, 130 malignancy patients were analyzed, 82 (63%) males. The mean age of the patients was 5.9 ± 4.31 years. Among these patients, 103 (79.2%) were under ten. ALL was the most common malignancy, accounting for 42.3% of cases. In that order, the most frequent liver-related manifestations observed in patients with malignancies were hepatomegaly, splenomegaly, and abdominal distension. Gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and jaundice in patients with malignancy may be caused by tumor pressure effects, liver metastasis, hepatitis, gastritis, pancreatitis, infections, or side effects of chemotherapy drugs [17-19].

A study by Segal et al. [20] reported that one-third of patients had abnormal liver enzyme levels at diagnosis, with 52% exhibiting ALT levels more than twice the normal range. Their findings suggested that leukemic infiltration of the liver contributes to liver damage and subsequent elevation of liver enzymes. The identified risk factors for hepatic dysfunction in their study included older age, higher white blood cell count at diagnosis, T-cell leukemia, and bulky disease. Similarly, in the present study, approximately one-third of patients with ALL and 22% of those with AML showed elevated ALT levels. In Nepal, Sharma et al. [21] conducted a study on 158 patients with leukemia, revealing that those with leukocytosis were more prone to splenomegaly and hepatic dysfunction. Elevated AST and ALT levels were noted in 16% and 34% of patients. Another study by Tsai et al. [22] found that higher AST levels and hypoalbuminemia were poor prognostic factors in cancer patients receiving palliative care. Their findings also indicated a correlation between prolonged prothrombin time and cancer progression. While acute liver failure is uncommon in ALL, a few cases have been documented. Hyperbilirubinemia, though not a typical early manifestation of ALL, has also been reported in rare cases [23]. In the current study, no cases of liver failure were observed at the time of diagnosis, and hyperbilirubinemia was not a common finding.

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Conclusion

The findings of our study indicate that clinical and laboratory signs of liver involvement are highly prevalent in children with malignancies. This involvement can be critical in assessing disease progression and informing treatment strategies. Abnormalities in liver function tests may signal liver damage or involvement, highlighting the importance of regular testing.

Ethical Considerations

Approved by the Zahedan University Ethics Committee (Ethics Code: IR.ZAUMS.REC.1395.98).

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None.

Conflict of Interest

The authors declare no conflicts of interest.

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Authors' Contributions

G.M.A: Study concept, study design, manuscript writing, and literature search; H.A.K: Literature search and manuscript editing; S.M.N.T: Manuscript editing; A.K: Manuscript editing; Z.N.N: Literature search and manuscript editing. R.R.K: Data acquisition and statistical analysis.

References

[1]. Jorjani G, Roshandel G, Taherian MR, Mirbehbahani N, Moaddabshoar L, Ahmadi A, et al. Epidemiology and geographical patterns of common childhood cancers in Iran: Evidence from the National Cancer Registry. Cancer Epidemiol. 2024; 93:102685.

[2]. Michel G, Von Der Weid NX, Zwahlen M, Redmond S, Strippoli M, Kuehni CE, et al. Incidence of childhood cancer in Switzerland: The Swiss childhood cancer registry. Pediatr Blood Cancer 2008; 50(1): 46-51.

[3]. Hassanipour S, Fathalipour M, Delam H, Ghorbani M, Abdzadeh E, Arab-Zozani M, et al . The incidence of childhood cancer in Iran: A systematic review and meta-analysis. Iran J Ped Hematol Oncol. 2019; 9 (3): 193-206.

[4]. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010; 28: 2625-634.

[5]. Huang FL, Liao EC, Li CL, Yen CY, Yu SJ. Pathogenesis of pediatric B-cell acute lympho-blastic leukemia: Molecular pathways and disease treatments. Oncol Lett. 2020; 20(1): 448-54.

[6]. Hunger SP, Mullighan CG. Acute lympho-blastic leukemia in children. New Engl J Med. 2015; 373(16): 1541-552.

[7]. Izadi M, Fazel M, Saadat SH, Taheri S. Hepatic involvement by lymphoproliferative disorders post liver transplantation: PTLD. Int Survey Hepatol. 2011; 5(3): 759-66.

[8]. Leite NP, Kased N, Hanna RF, Brown MA, Pereira JM, Cunha R, et al. Cross-sectional imaging of extranodal involvement in abdominopelvic lymphoproliferative malignancies. Radio Graphics. 2007; 27(6): 1613-634.

[9]. Tomasian A, Sandrasegaran K, Elsayes KM, Shanbhogue A, Shaaban A, Menias CO. Hematologic malignancies of the liver: spectrum of disease. Radiographics 2015; 35(1): 71-86.

[10]. Powell N, Rusli F, Hubscher SG, Karanth M, Mutimer D. Adult T-cell leukemia presenting with acute liver failure. Leuk Res. 2006; 30(10): 1315-317.

[11]. Davis M L, Hashemi N. Acute liver failure as a rare initial manifestation of peripheral T-cell lymphoma. World J Hepatol. 2010; 2(10): 384-86.

[12]. Belgaumi AF, Hudson MM. Childhood acute lymphoblastic leukemia presenting with severe hepatic dysfunction. Med Pediatr Oncol. 2001; 37(2): 142-44.

[13]. Rivet C, Leverger G, Jacquemin E, Bernard O. Acute leukemia presenting as acute hepatitis without liver failure. J Pediatr Gastroenterol Nutr. 2014; 59(5), 640-41.

[14]. Shahriari M, Shakibazad N, Haghpanah S, Ghasemi K. Extramedullary manifestations in acute lymphoblastic leukemia in children: a systematic review and guideline-based approach of treatment. American Journal of Blood Research 2020; 10(6): 360.

[15]. Murakami J, Shimizu Y. Hepatic manifestations in hematological disorders. Int J Hepatol. 2013; 2013: 1-13.

[16]. Miri-Aliabad G, Dahmardeh H. Obstructive jaundice due to pancreatic head mass: A rare and

[DOI: 10.18502/ijml.v11i2.18136]

unusual presentation of acute myeloid leukemia in children. Turk Arch Pediatr. 2021; 56(5): 530-32.
[17]. Miri-Aliabad G, Asgarzadeh L, Niazi A. Advanced gastric adenocarcinoma in a 12-year-old girl. Iranian Journal of Pediatrics 2021; 31(4): 108870.
[18]. Devarapalli UV, Sarma MS, Mathiyazhagan G. Gut and liver involvement in pediatric hemato-lymphoid malignancies. World J Gastrointest Oncol. 2022; 14(3): 587-606.
[19]. Miri-Aliabad G, Dahmardeh H. Acute pancreatitis as a rare and unusual manifestation of COVID-19 in a child with acute lymphoblastic leukemia. Int J Cancer Manag. 2023; 16(1): 123515.
[20]. Segal I, Rassekh SR, Bond MC, Senger C, Schreiber RA. Abnormal liver transaminases and conjugated hyperbilirubinemia at presentation of acute lymphoblastic leukemia. Pediatr Blood Cancer 2010; 55: 434-39.
[21]. Sharma PB, Karki L. Abnormal hepatic function and splenomegaly on the newly diagnosed acute leukemia patients. J Nepal Med Assoc. 2007; 46(168): 165-69.
[22]. Tsai HJ, Hsieh MY, Tsai YC, Liu ZY, Hsieh HY, Lee CM, et al. Liver function tests may be useful tools for advanced cancer patient care: a preliminary single-center result. Kaohsiung J Med Sci. 2014; 30:146-52.
[23]. Felice MS, Hammermuller E, De Dávila MT, Ciocca ME, Fraquelli LE, Lorusso AM, et al. Acute lymphoblastic leukemia presenting as acute hepatic failure in childhood. Leuk Lymphoma 2000; 38(5-6): 633-37.

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