Pediatr Gastroenterol Hepatol Nutr. 2024 Jul;27(4):215-223
https://doi.org/10.5223/pghn.2024.27.4.215
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

Association between Transfusion-Related Iron Overload and Liver Fibrosis in Survivors of Pediatric Leukemia: A Cross-Sectional Study

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Received: Jan 29, 2023
Revised: Apr 20, 2024
Accepted: May 15, 2024
Published online: Jul 8, 2024

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ABSTRACT

Purpose: Patients who receive frequent blood transfusions are at an elevated risk of developing hepatic fibrosis due to iron overload in the liver. In this study, we evaluated the effectiveness of transient elastography (TE) (FibroScan®) for assessing liver fibrosis in patients with pediatric cancer.
Methods: We enrolled 106 consecutive cases of acute leukemia in individuals under 21 years of age. The participants were followed for 2 years. Based on their serum ferritin (SF) levels, the patients were divided into two groups: group 1 (SF≥300 ng/mL) and group 2 (SF<300 ng/mL). A liver FibroScan® was performed, and a *p*-value of less than 0.05 was considered statistically significant.
Results: Among the various parameters in the liver function test (LFT), alkaline phosphatase was significantly higher in a subgroup of patients aged 5–8 years in group 2 compared to those in group 1. The indices of liver fibrosis determined by TE, including the FibroScan score, controlled attenuation parameter score, steatosis percentage, and meta-analysis of histological data in viral hepatitis score, as well as indirect serum markers of liver fibrosis such as the aminotransferase (AST)/alanine aminotransferase (ALT) ratio, Fibrosis 4 score, and AST to platelet ratio index, did not differ significantly between the two groups. The association between the TE results and LFT parameters was only significant for ALT.
Conclusion: Transfusion-associated iron overload does not have a significant correlation with severe liver fibrosis. FibroScan® is not a sensitive tool for detecting early stages of fibrosis in survivors of pediatric leukemia.

Keywords: Iron overload; Leukemia; Liver function tests; Blood transfusion; Liver cirrhosis

INTRODUCTION

Iron plays a vital role in the normal functioning of human cells. Moreover, iron is primarily stored in hepatic cells as ferritin, which makes up one-third of the total iron pool. The remaining two-thirds is present in hemoglobin, which is responsible for transporting oxygen in the bloodstream [1]. Under normal conditions, iron absorption and loss are balanced at 1–2 mg/day. Apart from the shedding of the gastrointestinal mucosa and the menstrual cycle,

Funding

This study was supported by Shiraz University of Medical Sciences with grant number 93-01-01-8755.

Conflict of Interest

The authors have no financial conflicts of interest.

no other physiological mechanisms eliminate excess iron from the body [2]. The organs most susceptible to iron overload (IO) are the heart, liver, and endocrine system. The liver has the highest rate of iron loading and unloading, followed by the pancreas and heart [2]. In addition to inflammation, fibrosis, and cirrhosis, liver IO can also lead to hepatocellular carcinoma (HCC) [1].

Patients with transfusion-dependent anemias are prone to IO and its various clinical sequelae [3]. Liver failure is a major cause of death in the aforementioned patients due to prolonged excess iron accumulation. Accurate assessment of overall iron status and timely initiation of chelation therapy is critical in preventing irreversible damage to the organs. The prognosis hinges on the extent of liver iron accumulation and fibrotic changes [4]. Pediatric patients undergoing treatment for hematologic cancers often receive blood transfusions, resulting in iron accumulation in the body, especially in the liver. This can lead to debilitating fibrosis in these young patients [5].

Various approaches are used to assess the degree of liver fibrosis. Transient elastography (TE), commonly known as FibroScan®, has been employed by clinicians to evaluate chronic viral liver infections, such as chronic hepatitis C [6], chronic hepatitis B [7], and co-infection of hepatitis C and human immunodeficiency viruses [8,9]. Additionally, researchers have sought to investigate the efficacy of TE for fibrosis staging in non-viral chronic liver diseases, including primary biliary cirrhosis, primary sclerosing cholangitis [10], Wilson disease [11], hemochromatosis [12], chronic alcohol abuse [13], and fatty liver [14], the risk of development and recurrence of HCC after curative treatment in the context of chronic liver diseases [15], as well as the risk of methotrexate-induced hepatotoxicity in patients with rheumatoid arthritis, inflammatory bowel disease [16,17], or psoriasis [18]. Despite the utility of TE, liver biopsy and magnetic resonance imaging (MRI) are the most well-established imaging methods. They are considered the gold standard for evaluating liver fibrosis [19]. In contrast, liver FibroScan® is an innovative ultrasound technology that can estimate hepatic fibrosis by assessing liver stiffness. This technique relies on changes in tissue elasticity caused by hepatic fibrosis. Consequently, the technique is widely regarded as a non-invasive, safe, rapid, reproducible, and reliable method for assessing hepatic fibrosis and diagnosing liver cirrhosis [12,20].

Patients with leukemia are at risk of IO due to repeated blood transfusions during the early phase of their treatment and intensive chemotherapy. This can lead to the deposition of iron in the liver and the development of liver fibrosis. Acknowledging the significance of establishing a reliable, low-cost, non-invasive method for evaluating liver fibrosis in pediatric oncology patients, we conducted this study to investigate the effectiveness of TE in detecting liver fibrosis in pediatric patients with leukemia who have IO due to transfusions. Additionally, we aimed to identify any potential correlations between TE results and other relevant laboratory characteristics.

MATERIALS AND METHODS

In this cross-sectional study, a total of 106 pediatric patients diagnosed with acute leukemia were included. The patients were selected consecutively from an outpatient oncology clinic affiliated with Shiraz University of Medical Sciences, located in the south of Iran. The study was conducted between September 2014 and December 2016.

All the patients included in the study were in the maintenance phase of treatment for acute leukemia and were in complete bone marrow remission. None of the patients demonstrated any evidence of liver involvement associated with leukemia. Eligibility was confirmed by a pediatric gastroenterologist who assessed the patients. Patients with physical signs or laboratory and imaging findings indicating chronic liver diseases were excluded from the study. Additionally, screening for hepatitis B and C viruses, autoimmune hepatitis, and Wilson disease was conducted as requested by the consulting pediatric gastroenterologist.

Demographic data, including age, sex, duration of the disease, type of leukemia, volume of transfused packed cells per body weight, and laboratory test results, were collected for each patient. The parents of the patients were thoroughly informed about the study and required to provide written informed consent before their children could participate. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences under the code number IR.SUMS.MED.REC.1394.52.

At the onset of the study, we measured serum ferritin (SF) in the fasting state using the ElectroChemiLuminescence method (Hitachi cobas E411). If a participant had a febrile illness, we postponed the test until 2 weeks after the infection had completely resolved. Based on the SF levels, we divided the patients into two groups. Group 1 consisted of patients with SF levels ≥300 ng/mL, while patients with SF levels less than 300 ng/mL were allocated to group 2. Notably, none of the patients with IO had a history of iron chelation therapy. Furthermore, comprehensive blood count (CBC) and liver function tests (LFT) were conducted, encompassing assessments of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, total protein, and albumin. We categorized the patients into four age groups (1–4 years, 5–8 years, 9–13 years, and 14 years and older), and age-adjusted parameters such as ALP and CBC were compared within the respective age groups.

We measured liver stiffness in all patients using FibroScan® (Echosens). The measurement was obtained while the patient was lying in a dorsal decubitus position, with the arms in maximal abduction. We conducted the measurements in the right and left intercostal spaces. We expressed liver stiffness (FibroScan score) in kilopascals (kPa) and computed it for each participant as the median of 10 validated measurements, following the manufacturer's instructions. We considered measurements with an interquartile range of <30% of the median value and a success rate of >60% as reliable. We also performed two-dimensional shear wave elastography (SWE) studies using the Aixplorer ultrasound system (SuperSonic Imagine SA) with a convex broadband probe (SC6-1, Super-Sonic Imagine). This technique offers the advantage of being compatible with ultrasound machines, allowing for easy probe installation. During the SWE examination, we asked the patients to hold their breath for 3 to 4 seconds. We recorded liver stiffness in the right lobe while the patient was lying in a dorsal decubitus position, following the protocol used for FibroScan®. We placed an SWE box 1.5 to 2 cm away from the Glisson capsule and on the liver parenchyma to avoid measuring large vessels. For quantitative measurements, we placed a round region of interest inside the SWE box and recorded the minimum and maximum values of stiffness, expressed in kPa. We conducted four measurements and recorded the median value. We used the meta-analysis of histological data in viral hepatitis (METAVIR) fibrosis score, which is graded on a 5-point scale from 0 to 4, to determine the degree of fibrosis. Controlled attenuation parameter (CAP) score measures the increased attenuation of ultrasound waves when travelling through

steatotic hepatic tissue, compared to normal liver. It is reported in dB/m. Steatosis degree shows the percent of affected hepatocytes.

We calculated some non-invasive serum markers of liver fibrosis as follows: AST to platelet ratio index (APRI)=[(AST/45)/platelet count]×100. Fibrosis 4 (FIB-4) score=(age×AST)/(platelet count×ALT 2).

We considered an APRI score less than 0.05 as indicating mild or no fibrosis, while values higher than 1.5 were considered indicative of advanced fibrosis. For the FIB-4 score, we set a cut-off point of 1.45 to distinguish between nil/mild and severe fibrosis.

Sample size calculation

Given α=0.05, power=90%, and effect size (r)=0.3 [12,21], a minimum of 106 patients was calculated to be sufficient for the study. Data were analyzed using SPSS software, Windows version 21 (IBM Co.). Quantitative and categorical variables were compared between the two groups using the Student's *t*-test and the chi-square test, respectively. The correlation between SF levels and TE was determined using Pearson's correlation test. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

A total of 106 consecutive pediatric oncology patients were studied over a 2-year follow-up period. The age of the patients ranged from 1 to 21 years (mean±standard deviation: 7.74±4.51). Female patients comprised 40.6% (n=43), while 59.4% (n=63) were male. The majority of patients were affected by acute lymphoblastic leukemia, accounting for 95.3% (n=101), while only 4.7% (n=5) had acute myeloid leukemia. Approximately, 66 patients with SF≥300 ng/mL (group 1) and 40 patients with SF<300 ng/mL (group 2) were included. The laboratory values are summarized in **Table 1**.

Patients with higher SF demonstrated significantly lower platelet counts compared to the count in those with normal SF levels (p=0.006). However, when the sample was stratified by age, the correlation lost its significance. In addition, the LFT results were comparable in both groups, except for ALP, which was higher in pre-pubertal patients aged 5–8 years with normal SF levels compared to the levels in those with higher SF levels (p=0.01).

Table 2 summarizes the scores measured by TE, as well as the indirect serum markers of liver fibrosis. None of the measured scores or serology markers were significantly different between the two studied groups. Regarding the METAVIR score, the majority of patients had mild or no fibrosis in either group (F0/F1), and a minority were classified in the F2 zone. None of the patients in either group had METAVIR scores, indicating severe fibrosis (F3/F4).

Bivariate Pearson correlation analysis demonstrated that the FibroScan® score and METAVIR score were significantly correlated with ALT, but not with other components of the LFT (r=0.214, p=0.028 and r=0.3, p=0.01, respectively) (**Table 3**). SF was also significantly correlated with the amount of transfused blood (r=0.34, p<0.001). Other variables, including the duration of illness and the amount of transfused packed red blood cells (PRBC), were not correlated with FibroScan® results (r=0.17, p=0.082 and r=0.185, p=0.057, respectively).

https://doi.org/10.5223/pghn.2024.27.4.215

Table 1. Comparison of the laboratory values in patients with leukemia with high and normal serum ferritin levels

Parameter	Mean±SD (min-max)	Group 1 (mean±SD, n=66)	Group 2 (mean±SD, n=40)	Mean difference (95% CI)	*p*-value
Duration of illness (m)	26.8±14.9 (5.0–88.0)	24.6±15.6	30.5±13.0	−5.8 (−11.7 to −0.01)	0.049
Transfused PRBCs (mL/kg)	74.4±71.0 (0.0–380.0)	88.7±77.8	52.1±52.5	36.6 (11.0 to 62.2)	0.006
Serum ferritin (ng/mL)	643.6±714.1 (6.7–3,548.0)	950.6±752.2	137.1±85.9	813.4 (626.7 to 1,000.2)	<0.001
WBC (/mm^3)	3,709.7±1,842.0 (800–11,700)	3,865.6±1,838.8	1,841.4±291.1	413.1 (−317.9 to 1,144.1)	0.26
Age (yr)					
1–4		4,761.5±2,305.6	3,793.7±2,531.7	967.7 (−896.8 to 2,832.4)	0.29
5–8		3,010.9±1,356.9	3,417.3±1,227.2	−406.4 (−1,229.1 to 416.2)	0.32
9–13		4,466.1±1,801.6	2,280.0±990.1	2,186.1 (−77.3 to 4,449.6)	0.058
≥14		3,584.6±1,530.7	2,815.0±445.4	769.6 (−1,652.1 to 3,191.3)	0.50
Hemoglobin (g/dL)	11.9±1.5 (6.0–16.7)	11.9±1.7	11.8±1.3	0.1 (−0.4 to 0.7)	0.67
Age (yr)					
1–4		11.58±1.43	11.24±1.43	0.3 (−0.7 to 1.4)	0.53
5–8		11.68±1.52	12.38±1.04	−0.7 (−1.5 to 0.1)	0.09
9–13		12.7±1.4	12.2±0.9	0.4 (−1.3 to 2.3)	0.59
≥14		11.9±2.4	11.5±1.8	0.4 (−3.4 to 4.3)	0.82
Platelet count (×10^3)	279±125 (15–1,069)	254.19±142.62	322.27±75.30	−68.0 (−116.4 to −19.6)	0.006
Age (yr)					
1–4		303.46±246.87	345.38±75.47	−41.9 (−175.1 to 91.3)	0.52
5–8		292.59±108.62	313.16±78.15	−20.5 (−81.2 to 40.1)	0.49
9–13		212.0±74.4	293.3±48.8	−81.3 (−175.4 to 12.7)	0.08
≥14		198.3±96.8	267.5±50.2	−69.1 (−223.4 to 85.2)	0.35
AST (U/L)	37.54±28.46 (12.0–218.0)	30.03±34.18	35.07±14.97	3.9 (−7.3 to 15.3)	0.49
ALT (U/L)	45.88±57.69 (6.3–386.0)	51.24±68.24	37.02±32.74	14.2 (−8.6 to 37.0)	0.22
ALP (U/L)	504.93±199.14 (133.0–1,250.0)	486.13±224.17	535.95±146.37	−49.8 (−121.2 to 22.6)	0.17
Age (yr)					
1–4		459.69±190.77	522.19±141.36	−62.4 (−189.0 to 64.0)	0.32
5–8		435.23±152.68	555.05±129.28	−119.8 (−210.0 to −29.6)	0.01
9–13		591.2±259.9	533.6±328.0	57.6 (−292.1 to 407.3)	0.73
≥14		453.1±275.7	468.0±22.6	−14.8 (−449.6 to 419.9)	0.94
Albumin (g/dL)	4.39±0.49 (3.0–5.4)	4.34±0.52	4.45±0.42	−0.1 (−0.3 to 0.08)	0.26
Total protein (g/dL)	6.92±0.72 (4.8–8.7)	6.88±0.80	6.99±0.59	−0.1 (−0.3 to 0.1)	0.43
Total bilirubin (mg/dL)	0.78±0.37 (0.2–2.6)	0.81±0.40	0.72±0.30	0.09 (−0.05 to 0.2)	0.22
Direct bilirubin (mg/dL)	0.21±0.12 (0.1–0.8)	0.22±0.19	0.13±0.09	0.02 (−0.01 to 0.07)	0.22

Group 1: serum ferritin ≥300 ng/mL, group 2: serum ferritin <300 ng/mL, PRBC: packed red blood cells, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

Table 2. Comparison of FibroScan® indices and non-invasive serum markers of fibrosis in patients with leukemia with high and normal serum ferritin levels

Parameter	Group 1 (n=66)	Group 2 (n=40)	*p*-value
FibroScan® score (kPa)	4.48±1.32	4.46±1.13	0.304
CAP score (dB/m)	192.46±54.48	167.75±46.37	0.714
Steatosis (%)	12.73±21.14	5.14±3.43	0.135
METAVIR score*	63 (95.5)	39 (97.5)	>0.999
AST/ALT ratio	1.31±0.63	1.30±0.63	0.187
APRI score (≤0.5)	56 (94.9) (7 missing data)	38 (100) (2 missing data)	0.278
FIB-4 score (<1.45)	65 (98.5)	39 (100) (1 missing data)	>0.999

Values are presented as mean±standard deviation or number (%).
Group 1: serum ferritin ≥300 ng/mL, group 2: serum ferritin <300 ng/mL, CAP: controlled attenuation parameter, AST: aspartate aminotransferase, ALT: alanine aminotransferase, APRI: AST to platelet ratio index, FIB-4 score: fibrosis 4 score.
*Numbers represent patients with mild/no fibrosis.

DISCUSSION

This study is the first to investigate the usability of TE for evaluating liver fibrosis in pediatric patients with leukemia with IO. As expected, the volume of transfused PRBC (mL/kg) was significantly high in the group with SF≥300 ng/mL. The patients with high SF also

https://doi.org/10.5223/pghn.2024.27.4.215

Table 3. Correlation analysis of FibroScan® indices with liver function test parameters

Variable	FibroScan® score		METAVIR score		CAP score		Steatosis percentage	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
AST	0.140	0.153	0.14	0.14	0.05	0.73	0.009	0.96
ALT	0.214	0.028*	0.30	0.01*	0.15	0.36	0.09	0.60
ALP	0.134	0.169	−0.01	0.89	−0.02	0.88	−0.14	0.43
Albumin	0.075	0.443	0.004	0.96	0.16	0.34	0.27	0.12
Total protein	0.037	0.710	0.06	0.53	−0.17	0.29	0.11	0.51
Total bilirubin	0.124	0.207	−0.03	0.69	−0.05	0.74	−0.007	0.96
Direct bilirubin	0.008	0.932	0.02	0.81	−0.16	0.33	0.05	0.76

CAP: controlled attenuation parameter, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase.
*Indicates statistical significance.

demonstrated low platelet counts. Although the correlation lost significance when the data were age-stratified, it may indicate severe bone marrow suppression requiring further transfusion support. Despite the data being within the normal range for children, the clinical significance of this association remains under debate.

LFTs were comparable in both groups with normal and high SF. Therefore, we stratified the study population into four age groups and compared ALP levels across these age strata, considering that ALP values differ during infancy, childhood, and adolescence. Although ALP levels did not differ between groups in the overall population, the level was higher in patients aged 5–8 years with normal SF levels compared to those in age-matched children with high SF levels. Given the normal range of ALP in both groups, we believe that this difference in serum ALP is not attributed to IO.

Regarding TE measurements, none of the patients in either group exhibited signs of advanced fibrosis. Most patients were in the mild or no fibrosis stage (F0–F1), and only a few patients were proven to be in the moderate stage of fibrosis (F2), with no statistical difference between the two groups ($p>0.99$). Additionally, although FibroScan score, CAP scores, and steatosis percentages were elevated in patients with iron load, the difference did not reach statistical significance (**Table 2**). This might be partly explained by the fact that the majority of our patients had early-stage liver fibrosis, and TE demonstrates sensitivity in detecting advanced stages of liver fibrosis [22]. Similarly, almost all participants in both groups had an APRI of <0.5 and a FIB-4 score of <1.45, indicating mild or no fibrosis. Thus, transfusion-related IO in patients with cancer is a transient process with no serious impact on the liver parenchyma.

The association between FibroScan® results with LFT items was only significant for ALT. Notably, increased SF levels alone are unlikely to cause advanced fibrosis, despite reports of mildly raised liver enzymes in patients. Moreover, evidence regarding the efficacy of FibroScan® for detecting liver fibrosis in transfusion-related IO is scarce. In a study by Voskaridou et al. [23], 110 patients with sickle cell disease were followed, and a strong correlation was identified between liver stiffness measured by FibroScan® and liver iron concentration (LIC) reported by T2*MRI. The study also demonstrated a correlation between liver stiffness measurements (LSMs) and factors such as SF, number of blood transfusions, hemoglobin, reticulocyte count, lactic dehydrogenase, bilirubin, and other indicators of liver function. The researchers concluded that iron chelation was associated with reduced LSM [23]. Similarly, Drasar et al. [24] discovered that TE was correlated with age, SF, number of transfused packed cells, and all components of LFTs. However, in our study, we did not observe any significant association between FibroScan® measurements and LFT components, except for ALT, nor with other variables such as the number of transfused packed cells. This

https://doi.org/10.5223/pghn.2024.27.4.215

variation might stem from the unique characteristics of patients with cancer with occasional transfusion needs, as opposed to patients with transfusion-dependent hemolytic anemia disorders such as sickle cell disease and other hemoglobinopathies, where hemolysis, ineffective erythropoiesis, and regular transfusions lead to significant iron deposition in vital organs, including the liver [25].

Mirault et al. [20] conducted a prospective study involving 15 chronically transfused patients and compared the TE results with the histological stage of fibrosis observed in liver biopsies. The study established that mean TE values significantly differed between patients with severe fibrosis and those with mild or no fibrosis. A TE value above 6.25 kPa indicates a patient's risk of severe fibrosis [20]. Another study involving patients with thalassemia revealed that TE had a sensitivity of 60% and specificity of 89% in detecting severe fibrosis. Additionally, TE was also associated with ALT, bilirubin, and gamma-glutamyl transferase levels [26]. These findings support our belief that TE can reliably predict significant fibrosis, although the parameter may not be as accurate in detecting the early stages of liver fibrosis [27].

Strengths and limitations

This study provides new information on the correlation between SF and liver fibrosis in a group of poly-transfused children with cancer. To our knowledge, this is the first study of its kind. We employed two non-invasive tools (TE and serum markers) to assess liver fibrosis in children with cancer, as invasive procedures such as liver biopsy pose significant challenges. This approach possibly improved the accuracy of our assessment. However, our study has limitations, including the relatively small sample size, short follow-up period, and lack of the use of liver biopsy for precise comparison and analysis. Employing MRI-based elastography for evaluating liver fibrosis would be useful, as the technique is more accurate than ultrasound-based elastography and may yield better results. Additionally, we did not assess LIC using a reliable and precise method, such as T2*MRI, which has been demonstrated to correlate well with liver biopsy [28]. Therefore, we recommend conducting further multi-center studies with prolonged follow-up periods to improve understanding of the long-term effects of IO on the development of liver fibrosis. Furthermore, correlating LSM with LIC measured by T2*MRI is expected to increase the accuracy of these assessments.

Conclusion

In pediatric patients with leukemia, transfusion-associated IO did not result in advanced liver fibrosis, at least in the short term. Overall, a mild elevation of ALT levels is expected in these patients. Nevertheless, further studies with long follow-ups, using precise imaging techniques such as MR elastography and T2*MRI, are needed to accurately assess the long-term consequences of transfusion-related iron deposition in pediatric patients with malignancy.

ACKNOWLEDGEMENTS

This study was conducted as the thesis of M. Sobhani for getting her MD degree. We would like to thank Mrs. Farmani for helping us to prepare the manuscript and Shirin Parand at the Hematology Research Center of Shiraz University of Medical Sciences for the process of submission.

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