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Association of Hepatic Fibrosis Measured by Transient Elastography with Ferritin Level of Patients with Transfusion Dependent Thalassemia in Iraq

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ABSTRACT

Background: Regular transfusions in thalassemia major lead to iron buildup, especially in the liver, causing oxidative damage and fibrosis. While liver biopsy remains the gold standard, transient elastography offers a reliable, non-invasive alternative for assessing fibrosis.
Objectives: To measure the correlation between hepatic fibrosis assessed by transient elastography with ferritin level in transfusion dependent thalassemia patients.
Materials and methods: A cross-sectional study that included 81 individuals with thalassemia major aged 12 years and older. Participants were collected from the thalassemia center in Najaf. The serum ferritin level, alanine transaminase (ALT) and aspartate transferase (AST) were analyzed from a blood sample obtained from the participants. A fibrosis score was measured in kilopascals (kPa) by transient elastography machine and categorized as (F0 to F1) which indicates absence or minimal hepatic fibrosis (2-7 kPa), (F2) score: Moderate hepatic fibrosis (8-9 kPa), (F3) Significant fibrosis (9-14 kPa); and (F4) score cirrhosis or severe hepatic fibrosis (14 kPa or higher).
Results: There were 81 participants, 41 men and 40 were women. The mean age of patients was 22 years. Our result showed about two-thirds of participants had mild fibrosis (F0-F2, 67.9%), while one-third had significant fibrosis (F3-F4, 32.1%). There was a significant correlation (P-value = 0.035) between serum ferritin and liver fibrosis measured by transient elastography. In addition, a statistically significant positive correlation between liver enzymes (ALT, AST) and hepatic fibrosis (P-value = 0.0001) was also confirmed.
Conclusion: This study demonstrated a significant linear relationship between serum ferritin levels and the degree of liver fibrosis, as assessed by transient elastography. Incorporating fibroscan, together with ferritin monitoring, may enhance early detection and management of liver complications in this high-risk population.
Keywords: Beta thalassemia major; Liver iron content; Ferritin; Transient elastography

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INTRODUCTION

Thalassemia denotes a category of hereditary genetic disorder characterized by insufficient or diminished production of globin chains. Mutations in the beta-globin chain led to β-thalassemia, which is regarded as the most predominant variant among Mediterranean, African, and Asian ethnicities [1].

In individuals with β-thalassemia major (β-TM), prolonged transfusion therapy to rectify anemia leads to detrimental iron accumulation. The degree of iron overload is typically proportional to the quantity of transfused units and is cumulative [2].

Excessive iron is very toxic to all human cells and can result in severe and irreversible organ damage, including liver cirrhosis (fibrosis), diabetes, heart disease, and hypogonadism. Hepatic fibrosis is directly correlated with age, the quantity of transfused units, and liver iron content (LIC) [3].

Excessive iron in the liver can result in hepatic fibrosis, a disorder marked by an abnormal accumulation of extracellular matrix proteins, potentially culminating in cirrhosis and hepatic failure. As many as fifty percent of individuals with β-thalassemia get hepatic fibrosis. There is variability in the degree and course of hepatic fibrosis in β-thalassemia, and the underlying mechanisms remain little understood [4].

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Currently, transient elastography (TE) functions as a reliable, noninvasive method for assessing liver fibrosis. This economical approach yields results comparable to a liver biopsy (the gold standard test for assessing liver fibrosis) with good sensitivity and specificity. An increased liver stiffness signifies a higher probability of hepatic fibrosis [5].

TE is a novel, quick, noninvasive method intended to assess hepatic fibrosis, utilizing a mechanical wave produced by vibration. The speed of the wave moving through the liver tissue helps measure how flexible the liver is, which can indicate the presence of hepatic fibrosis [6].

Serum ferritin levels are proposed as a marker of iron overload in β-thalassemia, as they indicate the amount of iron accumulated in the body. Research has demonstrated a correlation between serum ferritin levels and liver iron content, a significant risk factor for hepatic fibrosis and cirrhosis [7].

Accurate assessment of liver fibrosis requires liver biopsy, which is an invasive technique with many complications. Therefore, this study aims to investigate the relationship between serum ferritin levels and liver fibrosis as measured by fibroscan in patients with thalassemia major. Understanding the relationship between serum ferritin levels and hepatic fibrosis on fibroscan may provide valuable insights into the pathophysiology of liver fibrosis in β-thalassemia, potentially improving the diagnosis and treatment of this complication.

MATERIALS AND METHODS

This is a cross-sectional study performed in the Thalassemia Centre at AL-Zahraa Teaching Hospital in the Holy City of Najaf, Iraq. The study was conducted between October 2024 and April 2025. Eighty-one participants were enrolled in this study; all were cases of transfusion-dependent thalassemia patients attending the thalassemia center for blood transfusion. All participants received verbal information about the aim of the study, and informed consent was obtained from each patient prior to participation. Ethical approval for the study was granted by the Ethics Committee of the Department of Pathology and the College Council of Medicine, University of Babylon (Document number 6-11, dated 4 September 2024).

Data were collected from each patient using a specially designed questionnaire that included the patient's name, age, sex, frequency of transfusion, whether parents are related or not, splenectomy status, type of iron chelation therapy, past medical history and presence of active infection by direct interview with the patients.

The sample size was calculated according to the Kish and Leslie formula [$N = Z^2p(1-p)/d^2$], where N = sample size, Z = Z-score for the desired confidence level (1.96 for 95% confidence), p = assumed population prevalence of β-thalassemia patients, and d = margin of error (0.05). The prevalence of thalassemia in Iraq is estimated to be nearly 4%, according to the World Health Organization (WHO) [8]. A previous Iraqi study reported a prevalence of 37.1 per 100,000 population. However, in Iraq, the prevalence of thalassemia appears to be increasing slightly, despite a decline in incidence [9]. Based on the sample size calculation, a minimum of 59 participants was required. However, this study included 81 patients during the study period, which enhances the statistical power and validity of the findings.

Male and female patients aged 12 years and older with a confirmed diagnosis of thalassemia major based on high-performance liquid chromatography (HPLC) results were included in this study. Patients were excluded if they had a history of chronic liver disease (e.g., hepatitis B or C, or autoimmune liver disorders), were pregnant, had any active infection or fever, consumed alcohol, were diagnosed with diabetes mellitus, or had other hematological disorders such as sickle cell disease.

Five milliliters of blood were taken from each patient via venipuncture using a disposable 5 ml syringe under aseptic conditions prior to blood transfusion. This blood was subsequently stored in a gel tube for 30 minutes at room temperature. Following blood coagulation, the tubes were centrifuged at 3000 rpm for approximately 10 minutes, after which the serum was utilized for liver function tests and serum ferritin measurement. Ferritin was measured by Chemiluminescent Immunoassay (CLIA, Mindray CL900i immunoassay Analyzer, Mindray, China). Alanine transaminase (ALT), aspartate transferase (AST), total serum bilirubin (TSB), and alkaline phosphatase (ALP) were measured by a clinical chemistry analyzer (Monarch 240, Biorex Diagnostic, UK). The reference ranges for liver function tests were as follows: ALT 0–35 U/L; AST 0–45 U/L; TSB, 0.3–1.4 mg/dL; and ALP, 40–150 U/L. After blood sample collection, all patients were subjected to transient elastography by the fibroscan machine. The examination was carried out on the right lobe of the liver through the right 9th to 11th intercostal spaces. We conducted liver elastography examination using the FT100 Mini560/800 Shear Wave Quantificational Ultrasound Diagnostic System performed by a gastro-entero-hepatology specialist. Result expressed in kilopascals (kPa) as follows:

1. A fibrosis score of F0 to F1 indicates no or little hepatic fibrosis (2–7 kPa).
2. F2 score: Moderate hepatic fibrosis (8–9 kPa).
3. F3 score: Significant hepatic fibrosis (9–14 kPa).
4. F4: Cirrhosis (severe hepatic fibrosis) (14 kPa or greater). The maximum result is 75 kPa [10].

Data were analyzed utilizing Statistical Package for the Social Sciences (SPSS) version 30 software (IBM, New York, USA). Numerical data were displayed as mean and standard deviation. Categorical variables were represented as frequencies and percentages. The chi-square test was used to find the association between categorical variables. An independent sample t-test was used to compare the means of continuous variables. Correlation analysis was performed using Spearman correlation, with a P-value less than 0.05 considered statistically significant.

RESULTS

This study included 81 patients who were diagnosed with β-thalassemia. The patients' ages ranged from 12 to 41 years, with a mean age of (22.31 ± 6.56) years. The majority of the patients presented in two age groups: 10-19 years (n = 37, 45.7%), and 20-29 years (n = 33,40.7%). Male patients (n = 41,50.6%) are slightly higher than female patients. Around 80% of patients were the result of consanguineous marriage. The majority of patients had blood transfusions every two weeks (71.6%). Deferasirox (Exjade) is the most commonly taken oral medication by studied patients (59.3%). Regarding splenectomy, 56.8% of the participants were non-splenectomized (Table 1).

All liver enzymes of studied patients were mildly elevated where the mean of ALT was 35.7 ± 29.2, the mean of AST was 45.24 ± 30.6, mean of TSB 3.1 ± 2.13, and mean of ALP

Table 1. Characteristic of the 81 patients with β-thalassemia.

Characteristics	Number	%
Age (years)		
12–19	37	45.7%
20–29	33	40.7%
30–39	8	9.9%
40–49	3	3.7%
Sex		
Male	41	50.6%
Female	40	49.4%
Splenectomy status		
Splenectomized	35	43.2%
Non-splenectomized	46	56.8%
Consanguineous marriage of parents		
Parent are related	67	82.7%
Non related parent	14	17.3%
Transfusion frequency		
Every week	9	11.1%
Every 2 weeks	58	71.6%
Every 3 weeks	14	17.3%
Iron chelator		
Oral	48	59.3%
Intravenous	27	33.3%
Combined	6	7.4%

164.7 ± 126.3. In additions, the mean of serum ferritin was significantly elevated (3505 ± 2915.08) as shown in Table 2.

The result showed that about half of the patients had F0-F1 (46.9%). In terms of significant fibrosis, the current result showed that two-thirds of the patients had mild (F0-F2, 67.9%) fibrosis (Table 3).

There was a significant correlation between serum ferritin and liver fibrosis in the studied patients, where the serum ferritin was significantly higher in patients with significant fibrosis as compared with those who had no or mild fibrosis (P-value = 0.035) as illustrated in Figure 1.

A significant positive correlation between ALT level and fibrosis scores (P-value = 0.0001) was revealed (Figure 2). In addition, AST level has a positive correlation (P-value = 0.0001) with liver fibrosis (Figure 3).

A significant positive relationship was observed between ferritin level and ALT (P-value = 0.001). In addition, AST has a positive correlation (P-value = 0.001) with serum ferritin (Figure 4).

Table 4 shows no significant mean difference in serum ferritin (ng/ml) among β-thalassemia patients who had splenectomy as compared with patients who did not (P-value = 0.197).

Table 2. Mean, median and standard deviation (SD) of biochemical markers of the 81 patients. ALT= Alanine transaminase, AST = Aspartate transferase, TSB = Total serum bilirubin, and ALP = Alkaline phosphatase.

Biochemical markers	Reference range	Mean	Median	SD
ALT	0–35(u/l)	35.7	27.2	29.2
AST	0–45(u/l)	45.24	36.1	30.6
TSB	0.3–1.4(mg/dl)	3.1	2.6	2.13
ALP	40–150(u/l)	164.7	125	126.3
Ferritin	12–375(ng/ml)	3505	3005	2915.08

Table 3. Fibroscan findings of the 81 patients.

Fibroscan findings	Frequency	Percentage
F0–F1	38	46.9
F2	17	21
F3	21	25.9
F4	5	6.2
No or mild fibrosis (F0–F2)	55	67.9
Significant fibrosis (F3–F4)	26	32.1

DISCUSSION

β-thalassemia major is a hereditary blood disorder that requires lifelong blood transfusions, leading to iron overload and liver complications. The liver is especially vulnerable, as it stores excess iron, increasing the risk of hepatocellular injury and fibrosis [11]. Even though a liver biopsy is the best way to check for liver scarring, safer and easier methods like

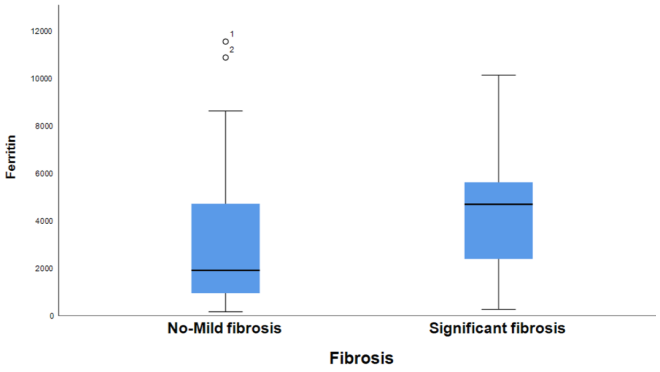

Figure 1. Boxplot diagram between serum ferritin and liver fibrosis. P-value = 0.035.

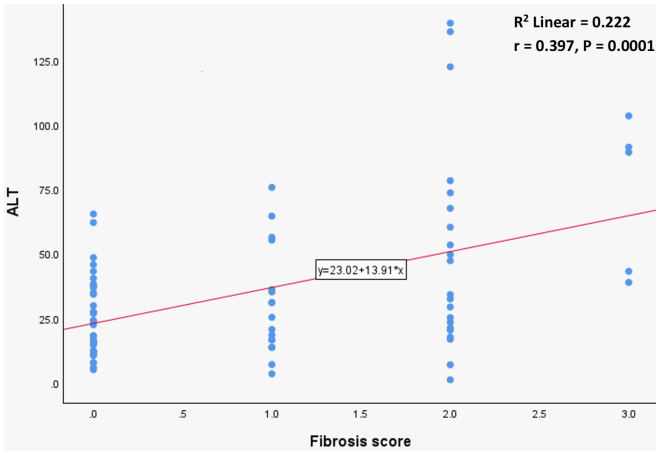

Figure 2. Scatterplot diagram between alanine transaminase (ALT) and fibrosis score.

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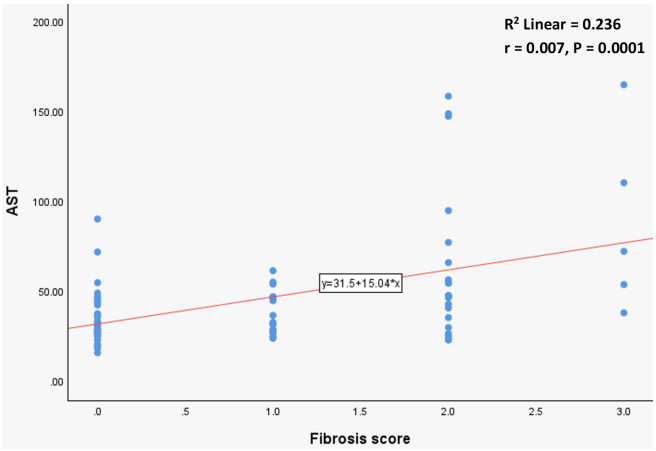

Figure 3. Scatterplot diagram between aspartate transferase (AST) and fibrosis score.

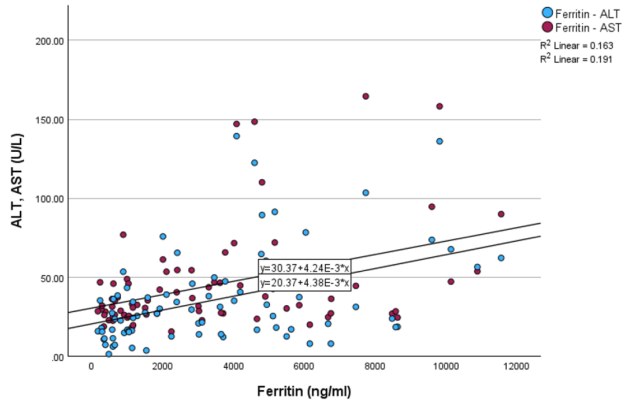

Figure 4. Scatterplot diagram between serum ferritin with alanine transaminase (ALT) and aspartate transferase (AST).

transient elastography, along with blood tests for ferritin and liver enzymes can be used instead. This study demonstrated a significant association between elevated serum ferritin levels and advanced fibrosis, underscoring the importance of close clinical monitoring and the implementation of timely, aggressive treatment strategies to prevent the progression of liver fibrosis in patients with thalassemia major.

The mean age of the studied participants was 22 years, ranging from 12 to 41 years. Male patients slightly outnumbered female patients. These findings are partially consistent with a study by Ansaf et al. in Iraq, which reported a mean patient age of 21 years and a male proportion of 51.3% [12]. Similarly, Ibrahim et al. in Egypt reported comparable results, with a mean patient age of 24 years and a slightly higher number of male patients [13].

This study found that 82.7% of patients were born to consanguineous (cousin) marriages, underscoring the genetic contribution to the prevalence of thalassemia. A closely related finding was reported by Hashim et al. in Iraq, who observed a consanguinity rate of 89.81%, aligning closely with the present results [14]. In addition, a study by Aziz et al. in Pakistan reported a comparable finding, with 79% of thalassemia patients being offspring of consanguineous (cousin) marriages

Table 4. Mean difference of serum ferritin (ng/ml) between splenectomized and non-splenectomized patients. SD = Standard deviation*.

Study variable	Patients group	Number	Mean	SD
Ferritin(ng/ml)	splenectomized	35	2835.97	2737.32
	Non-splenectomized	46	3593.72	2489.85

* P-value = 0.197.

[15]. However, a study in Bangladesh by Mahzabin et al. found that only 15% of patients had a history of consanguinity among their parents, and 85% of patients had an absence of consanguinity [16]. This difference may be because cousin marriages are very common and socially acceptable in Iraq; they are deeply rooted in tribal, cultural, and, at times, religious traditions. On the other hand, although cousin marriages do happen in Bangladesh, they are less frequent and socially discouraged than in Iraq.

The results of the current study were consistent with the findings of a study by Mohamed et al. in Egypt, which showed 47.1% of patients in F0-F1, 28.3% of patients in F2, 18.9% of patients in F3, and 5.7% of cases in F4 [10]. A Pakistani study by Ali et al. reported slightly different findings, with an F0–F1 fibrosis observed in 74% of patients, slightly higher than the proportion reported in our study. The same study noted F2 in 14.5%, F3 in 9.1%, and F4 in only 1.8% of cases [4]. Therefore, their F2, F3, and F4 stages were lower than this study. This difference may be attributed to the inclusion of thalassemia intermedia patients in their study, who generally require fewer transfusions than those with thalassemia major. Additionally, their smaller sample size and younger participant age group (mean age of 7 years) compared to our study (mean age of 22 years) may have contributed to the variation in fibrosis scores.

The result of this study revealed that ferritin was positively correlated with liver fibrosis, which matches the results of Ali et al. [4], Khan et al. [17], Atmakusuma et al. [18], and Mohamed et al. [10]. All studies showed that ferritin positively correlated with ferritin and hepatic fibrosis. In contrast, an Indian study done by Pipaliya et al. demonstrated that no correlation was seen between ferritin level and liver fibrosis [19]. This may be explained by the younger age of patients in their study (mean age of 12 years), which likely resulted in lower iron accumulation in the liver compared to the older participants in the current study.

The current study demonstrated a significant positive correlation between ALT and AST levels and the degree of liver fibrosis. These findings are consistent with the results of studies performed by Khan et al. in India [20], Ferraioli et al. [21] in Italy and Mohamed et al. [10] that found a positive significant correlation between liver enzymes (ALT, AST) and fibrosis score. Similarly, Yosef et al. in Egypt claimed that there were positive relationships between hepatic stiffness value assessed by fibroscan and the AST/ALT ratio among the studied patients. Regular monitoring of ALT and AST levels is essential, as elevated concentrations in the bloodstream reflect hepatocellular injury and help assess the extent of liver damage.

The result of the current study showed a significant positive correlation between serum ferritin with ALT and AST. It

could be explained by liver damage brought on by excessive iron buildup in thalassemia patients who have received numerous blood transfusions. These findings agree with the Iranian study by Saravani et al. [22] and Rabadiya et al. from India [23], which showed a significant correlation between serum ferritin and liver enzymes. Similarly, a study of Faruqi et al. in Pakistan showed ALT (more specific to hepatic tissue) had a more significant correlation than AST with serum ferritin [11].

In the present study, no significant difference in serum ferritin levels was observed between splenectomized and non-splenectomized thalassemic patients, suggesting that serum ferritin primarily reflects total body iron burden influenced by transfusion history and chelation therapy rather than splenectomy status. This agrees with the findings of the study by Wasan et al. in Iraq [24], Azeez et al. in Iraq [25], and Khawaji et al. in Saudia Arabia [26]. All studies reported no significant difference in mean serum ferritin levels between splenectomized and non-splenectomized patients. However, a study by Suebpeng et al. from Thailand found a significant difference in mean serum ferritin between the two groups [27]. They suggested that prolonged ineffective erythropoiesis in older patients led to increased intestinal iron absorption over time.

This cross-sectional study has several limitations. First, its design does not allow for establishing causal relationships between serum ferritin levels, liver enzymes, and liver fibrosis, as all were measured at a single point in time. Second, being a single-center study, it may not fully represent the broader population of patients with thalassemia major. Third, the connections seen might be affected by differences in how often patients receive blood transfusions, how well they follow their iron chelation therapy, or if they have any infections.

CONCLUSION

This study concluded that a clear linear relationship exists between serum ferritin levels and hepatic fibrosis, as measured by the fibroscan machine. Additionally, ALT and AST levels were identified as effective non-invasive tools for predicting fibrosis in thalassemia patients. These enzymes can thus serve as surrogate markers to monitor patients at high risk of developing fibrosis. The study also found a linear relationship between liver enzymes and serum ferritin, highlighting the importance of serial monitoring of liver function tests in thalassemia major patients, especially those with high serum ferritin levels. Regarding splenectomy history, no significant difference was found in serum ferritin levels between splenectomized and non-splenectomized patients.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

The study was conducted following the acquisition of informed consent from all participants. The study protocol received approval from the Ethical Committee of the College of Medicine, University of Babylon, under document number 6–11 dated 4 September 2024.

Consent for Publication

Not applicable. This manuscript does not contain any person's data in any form (including individual details, images, or videos).

Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All authors contributed to the study design. Gataa ZK drafted the manuscript and formatted the references using Endnote. All authors reviewed and approved the final version.

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