Original Article

Evaluation of the level of liver enzymes and its relationship with ferritin and the frequency of blood transfusion in patients with thalassemia

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ABSTRACT

Thalassemia major is the most common hemolytic anemia in Iran and the world that causes an increase in complications in patients, one of the most important of which is liver complications. Therefore, this study aimed to evaluate the level of liver enzymes and their relationship with ferritin and the frequency of blood transfusions in patients with thalassemia. This study was performed on 73 patients with thalassemia major. Demographic, clinical and laboratory information were recorded from the medical files. Data were analysed using SPSS version 22 software. Our study showed significant increasing trend in the AST, ALT and ALP levels in thalassemic patients. However, these changes were not statistically significant amount patients with different frequencies of blood transfusion ($p > 0.05$). Among liver enzymes, just AST and ALT had significant correlations with serum ferritin ($p < 0.001$). In addition, serum ferritin levels of more than 1625 mg/dl could predict the abnormal liver enzymes with the highest sensitivity (59%) and specificity (100%) when considering ALT and AST levels as diagnostic measures for liver problems. Due to the high prevalence of liver damage in thalassemia patients, serum ferritin in combination with the other factors can be applied as a suitable index for assessment of the liver function.

1. Introduction

A thalassemia is a group of hereditary disorders. Mutations causing this disease reduce the production of alpha-globin and β (beta) -globin chains [1]. β -thalassemia is also an autosomal recessive pattern disease and is more common than α - thalassemia. This disease is the result of various mutations in the beta-globin gene and leads to a decrease in the production of the beta-globin chain (β + thalassemia) or its absence (β 0 thalassemia). These mutations are mainly caused by point mutations in the beta-globin gene. If not treated, it can be fatal [2, 3]. Each year, over 50,000 new patients are born with

a severe form of thalassemia [4-6].

Thalassemia traditionally has a high prevalence in the Mediterranean area, countries in the Middle East, the Arabic peninsula and Southeast Asia [7, 8], so thalassemia mutations are among the Mediterranean, African, and Asian populations where malaria is endemic, it is more common. It seems that globin mutations in thalassemia are a protective factor against falciparum malaria [9].

In patients with beta-thalassemia major, an excessive increase in blood iron has been observed, which is due to chronic blood

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transfusion, ineffective erythropoiesis, increased abnormal absorption of iron from the intestine, and because the mechanisms of the human body do not have enough ability to eliminate excess iron, hemosiderosis (Hemosiderosis is a term used for excessive accumulation of iron deposits called hemosiderin in the tissues.) occurs. Also, serum ferritin levels can increase independently iron levels, which cause factors such as acute or chronic inflammation and acute or chronic liver damage [10, 11]. Serum ferritin levels may also increase due to frequent blood exchanges [12]. Since iron overload is the most common cause of morbidity and mortality in β-thalassemia major (β-TM), it is one of the main goals in the therapeutic management of the disease [13].

About 80% of transferred iron in the blood is captured by hepatocyte receptors, made up of a ferritin light chain [14, 15]. In fact, compared to other cells, hepatocytes not only synthesize the ferritin light chain as a part of the receptor but also secrete it into the blood as a serum protein [16], mainly at post-transcriptional levels, its secretion is regulated [17]. Studies have shown that increased liver iron levels may lead to hepatocyte damage. As a result, the iron released from the damaged liver tissue is transported through ferritin [18] and finally, during liver damage, the level of liver enzymes in the blood rises [19].

The most sensitive and widely used liver diagnostic enzymes are aminotransferases such as aspartate aminotransferase (SGOT or AST) and alanine aminotransferase (SGPT or ALT). These enzymes are usually located inside the liver cells, when the liver is damaged, ALT is released into the bloodstream and levels increase.

2. Materials and Methods

This was a cross-sectional descriptive-analytical study. Patients with beta thalassemia under the supervision of Zabol Thalassemia Center (2019-2020) and Amir Al-Momenin Hospital Zabol were visited by the researcher, blood samples were taken by the relevant doctor or colleagues.

Patients with beta-thalassemia under the supervision of Zabul thalassemia center (2019-2020) and Amir al-Momenin Hospital, Zabol were visited by the researcher, and blood samples were taken by the relevant doctor or colleagues. Then the samples were analyzed using research and laboratory kits for ferritin level and liver enzymes and the information was recorded.

2.1. People must have the following characteristics

2.1.1. Inclusion criteria

Thalassemia patients who have received blood at least once

2.1.2. Exit criteria

The presence of underlying diseases such as hepatitis and hemochromatosis or conditions such as infections and acute fever in patients with thalassemia who have not received blood.

According to the results of the study conducted by Momen and colleagues [19], the required sample size for estimating the serum ferritin levels in thalassemia patients, considering a standard deviation of 1572, a confidence level of 95%, a maximum error of 393, and a 20% dropout rate of samples, was determined to be 73 individuals. The factors needed to check the changes in liver enzymes and compared groups were collected in a researcher-made checklist. Ferritin and liver enzyme levels were measured by standard laboratory kits.

2.2. Statistical analysis

Quantitative and categorical data were described using mean (standard deviation) and percentage respectively. The differences in the mean of enzymes over time were assessed by the Wilcoxon test. Each time, these enzymes were compared in patients with different frequency of blood transfusion using the Mann-Whitney U test. Spearman's correlation coefficient was used to determine the correlation between serum ferritin and liver enzymes. ROC curve was used to determine the diagnostic accuracy of serum ferritin in predicting liver damage. The data was analyzed using SAS version 9.1 software.

3. Results

In this study, 73 patients with thalassemia were investigated, of which 39 (53.4%) were female. The average age of the patients was 11.1 with a standard deviation of 5.6. The minimum and maximum age of the participants was 2 years and 25 years, respectively. Mean ± standard deviation of serum ferritin of patients was 23.04±1375. The lowest and highest ferritin levels were 680 and 6950 respectively (table 1).

Table 1 shows that in people who received blood once a month, the average AST significantly increased from 40.9 to 66 mg/dL, (p=0.015). Also, in patients who received blood twice a month, the average AST increased from 62 to 77 mg/dL, which was also statistically significant (p=0.004). However, there was no significant difference in the amount of changes in AST level between the two groups of patients (p=0.166). 43.8% of patients received oral chelator, then 21.9% orally and by injection and 16.4% by injection. (Table 1). 87.7% of patients had injections twice a month and 12.3% once a month.

Table 1. The frequency of chelator consumption in the examined patients

P value For changes between two groups	P-value For earlier and later changes	Final AST mean± standard deviation	Initial AST mean± standard deviation (standard deviation)	Number of transfusions per month
0.166	0.015	66± 31	40.9±12.9	once
	0.004	77± 40	62±27	twice
		0.513	0.009	P value

Table 2 and figure 1 show that in people who received blood once a month, the average AST increased from 40.9 to 66 mg/dL, which was statistically significant (p=0.015). Also, in patients who received blood twice a month, the average AST increased from 62 to 77 mg/dL, which was statistically significant (p=0.004). However, there was no significant difference in the amount of changes in AST level in the two groups of patients with one and two monthly blood intakes (p=0.166).

Table 3 and figure 2 show that in people who received blood once a month, the average ALT increased from 36 to 56 mg/dL, which was statistically significant (p=0.012). Also, in patients who received blood twice a month, the average ALT increased from 71 to 80

mg/dL, which was statistically significant (p=0.049). However, there was no significant difference in the changes in the ALT level in the two groups of patients with one and two monthly blood intakes (p=0.462).

Table 2. Changes in mean AST in patients with different levels of blood intake

P-value For changes between two groups	P-value For earlier and later changes	Final ALT mean± standard deviation	Initial ALT mean± standard deviation	Number of transfusions per month
0.462	0.012	56± 33	36± 13	once
	0.049	80±41	71± 34	twice
		0.049	<0.0001	P value

In people who received blood once a month, the average ALP increased from 417 to 451 mg/dL, which was not statistically significant (p=0.594). In people who received blood once a month, the average ALP increased from 417 to 451 mg/dL, which was not statistically significant (p=0.594). However, there was no significant difference in the amount of changes in ALP level in two groups of patients with once and twice monthly blood collection (p=0.536).

Table 3. Comparison of changes in the average ALT in patients with different levels of blood intake

P value For changes of two groups	Pvalue For earlier and later changes	Final AST mean (standard deviation)	Initial AST mean (standard deviation)	Number of transfusions per month
0.462	0.012	56(33)	36(13)	once
	0.049	80(41)	71(34)	twice
		0.049	<0.0001	P value

Table 4 shows that there was a relatively high correlation between serum ferritin and AST level (0.53), which was statistically significant (p<0.001). Also, there was a relatively high correlation between serum ferritin and ALT level (0.45), which was statistically significant (p<0.001). However, a weak correlation was observed between ferritin and ALP levels (0.14), which was not statistically significant (p=0.219).

Table 5 shows that the area under the ROC curve for AST (figure 3) and ALT (figure 4) enzymes was higher than the ALP (figure 5). Also, the best cutoff points for serum ferritin to predict liver damage based on the increase of AST and ALT enzymes was equal to 1625

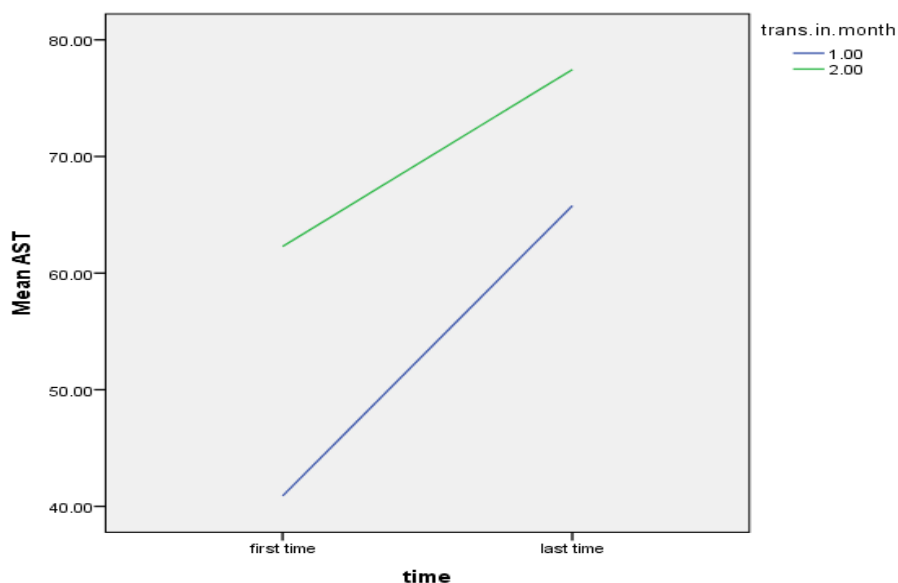mg/dL. The level under the curve was 0.7 based on ultrasound results.

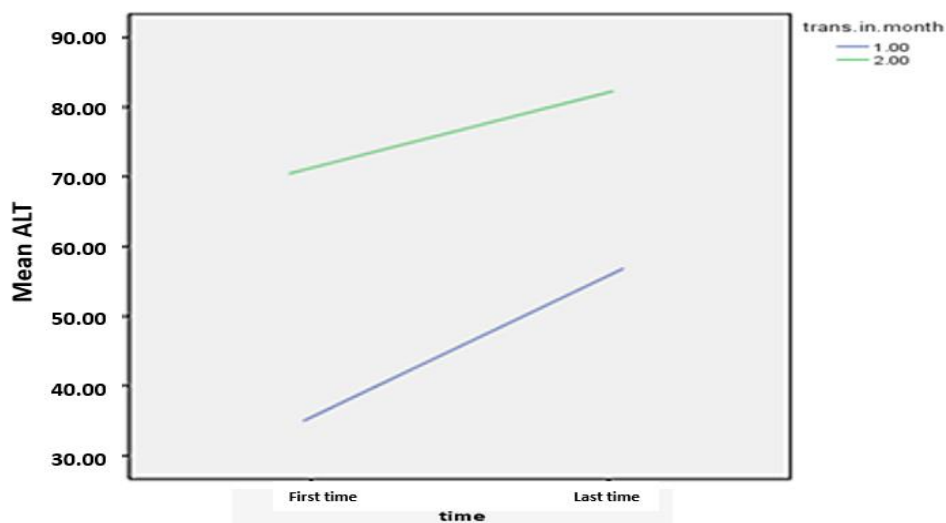**Fig. 1.** Comparison of changes in the average AST in patients with different levels of blood intake

Fig. 2. Changes in the average ALT in patients with different levels of blood intake

Table 4. Correlation between serum ferritin level and liver enzymes

P value	Raw correlation coefficient	Liver enzymes
<0.0001	0.53	AST
<0.0001	0.45	ALT
0.219	0.14	ALP

Table 5. Diagnostic accuracy of serum ferritin to predict liver damage in thalassemia patients

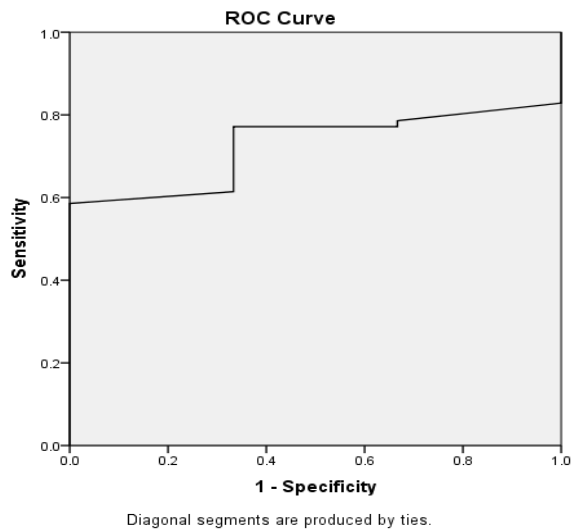| Feature	sensitivity	Optimal level of ferritin	The area under the AUC curve	Liver enzyme
100%	59%	1625	0.73 (0.59- 0.87)	AST
100%	59%	1625	0.71 (60- 82)	ALT
100%	4%	6280	0.51 (0.37- 0.65)	ALP
66%	80%	1625	0.74 (0.62- 0.86)	Sonography

Fig. 3. ROC curve of the accuracy of serum ferritin (AST) to predict the increase of liver enzymes
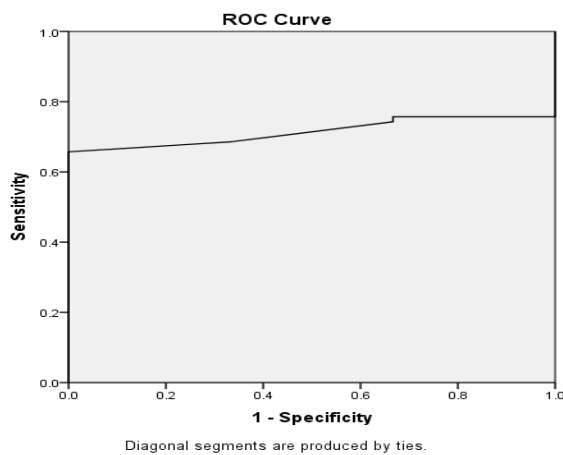

Fig. 4. ROC curve of the accuracy of serum ferritin (ALT) to predict the increase of liver enzymes
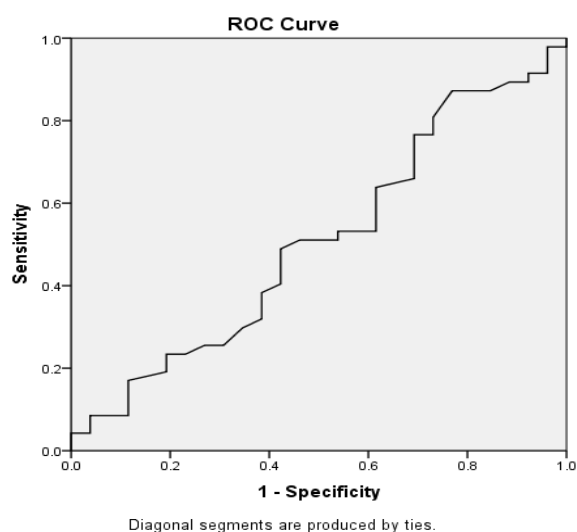

Fig. 5. ROC curve of the accuracy of serum ferritin (ALP) to predict the increase of liver enzymes

4. Discussion

In this study, we observed that although AST levels increased significantly over time in thalassemia patients, the changes in AST enzyme in thalassemia patients who received blood twice a month were similar to patients who received blood only once a month. Therefore, it does not seem that the amount of blood intake has an effect on AST changes.

Also, we observed that although ALT levels increased significantly over time in thalassemia patients, the changes in ALT enzyme in thalassemia patients who received blood twice a month were similar to patients who received blood only once a month. Therefore, it does not seem that the amount of blood intake has an effect on ALT changes. In addition, we found similar results regarding the changes of ALP levels among the two groups indicating that the changes of this enzyme were not related to the frequency of blood transfusion[6, 20-23].

In has been reported that the increase of liver enzymes in patients with thalassemia was investigated. 50% of patients were anti-HCV positive and 55% were HCV-PCR positive. Patients with high ALT and AST levels had significantly higher mean serum ferritin than patients with normal levels. However, in this study, these levels were not related to the number of injections per month but were related to the accumulation of ferritin in the long term[24]. The findings of the mentioned study are in consistent with the findings of our study. In our study, it was also found that the serum level of liver enzymes increases significantly in thalassemia patients and has a significant relationship with ferritin level, but not with the number of injections. And it seems that liver damage in patients is caused by iron accumulation and increased ferritin load [25-27].

In has been reported that the increase of liver enzymes was investigated among 65 subjects including 35 beta thalassemic patients and 30 healthy volunteers who were matched based on age and sex. AST and ALT levels in beta-thalassemia patients increased significantly (p < 0.001, respectively) compared to the control group. On the other hand, no significant difference was observed

in TP and ALB levels in beta-thalassemia patients. There was a negative correlation of hemoglobin level with AST (r = -0.4; p < 0.05) and ALT (r = -0.5; p < 0.01) levels, while there was no correlation with TP (r = 0.3; p < 0.05) and ALB (r). Abnormal levels of AST and ALT are present in beta-thalassemia patients. Elevated AST and ALT levels indicate that beta-thalassemia patients are at increased risk of heart and liver dysfunction [28]. Although there was no control group in our study to compare with thalassemia patients, the findings regarding the increase in liver enzymes in thalassemia patients are similar to our findings. It seems that patients with thalassemia suffer from liver damage in the long term. In our study, due to defects in the medical records, it was not possible to check the total protein, which requires a more detailed investigation in future studies.

The results of this study showed that the serum ferritin level had a significant correlation with the liver enzymes AST and ALT, while there was no significant relationship with the ALP enzyme level. Accordingly, the ROC curves showed that serum ferritin was only suitable for predicting liver damage based on the increase of AST and ALT [21, 25, 29-31]. On the other hand, considering 1625 mg/dl as the optimal cut point, the accuracy of serum ferritin for predicting liver damage based on abnormal AST and ALT levels was in line with the sonographic results. The difference was higher sensitivity for sonography and higher specificity for liver enzymes when used as a diagnostic measure for liver damage. Liver iron concentration is associated with parenteral iron intake, type and compliance with chelation therapy [21, 25, 31]. In transfusion-dependent thalassemia major, liver iron overload is one of the major problems of liver disease progression, and due to the regular regimen of blood transfusions, it leads to iron overload [32]. Fraquelli and colleagues [33] reported that liver damage increases with higher ferritin levels in thalassemia major patients.

In this study, Serum ferritin levels were evaluated as a potential surrogate marker for liver damage and showed a positive correlation with liver enzymes. There is a controversy regarding the relationship between serum ferritin and liver fibrosis [34]. The data show that there is a strong correlation between serum ferritin and the degree of liver fibrosis in thalassemia major patients. However, studies show that serum ferritin levels alone are not enough to evaluate the degree of fibrosis in thalassemia major patients. Other researchers showed that there is no relationship between the amount of liver damage and the amount of iron overload in beta-thalassemia major patients [35, 36]. The difference in the obtained results may be due to the difference in sampling, inclusion and exclusion criteria, control of confounders and sample size.

It has been determined that a range for liver ALT enzyme and serum ferritin level, which was the best time to start treatment with iron chelates in moderate thalassemia patients. They also found that there was a significant relationship between iron overload, serum ferritin and ALT levels, and also reported that high ferritin has a significant relationship with increased levels of liver enzymes [19]. The findings of the mentioned study are completely consistent with the findings of our study and show that there is a positive relationship between serum ferritin and the level of liver enzymes.

Un-transported iron (free iron) has been evaluated as an indicator of iron overload in thalassemia patients; Of course, this amount is limited in sickle cell patients [37-39]. It has been showed that the level of serum ferritin compared to free iron in the blood gives a better prognosis than the accumulated iron in the liver [27]. Although the level of serum-free iron was not investigated in our study, the findings regarding the significant relationship between serum ferritin and liver enzymes are completely consistent with the findings of our study, and it seems that the increase in serum ferritin level has a significant relationship with liver damage [25, 31, 40-42].

liver enzymes were investigated in thalassemia patients [43]. This study was conducted on 50 thalassemia patients and 50 age- and sex-matched control groups to investigate the change of serum AST and ALT and also whether this change can be related to

common hematological indicators. Compared to the control group, the liver enzymes of patients were significantly higher and there was a positive correlation between high ferritin and high levels of liver enzymes. In general, high levels of ferritin and liver enzymes may be important predictors of morbidity and mortality in thalassemia patients [43].

Although there was no control group in our study, the findings regarding the increase in the level of liver enzymes and its relationship with serum ferritin are completely consistent with the findings of our study. In our study, the complications and prognosis of patients and their relationship with laboratory findings, especially liver damage and ferritin level, were not investigated, which requires more detailed investigation in subsequent cohort studies. Absorption of iron from the gastrointestinal tract increases due to chronic anemia and erythropoiesis, as well as frequent blood transfusions with the occurrence of iron overload [44]. The increase in iron load and its effects on the liver are very different over time. Depending on the intensity of injection, administration of iron and absorption of iron in the gastrointestinal tract, which is strongly influenced by the severity of ineffective red blood cells and chronic anemia, liver damage occurs [45-47]. Serum ferritin levels also change according to changes in body iron load [10, 48, 49]. In this study, most subjects received regular blood transfusions. Hence, the mean serum ferritin levels were high.

In addition, iron distributed in the reticuloendothelial system (RES) increases ferritin synthesis and is released into the circulation, leading to elevated serum ferritin [12, 34, 35]. This highlights the importance of monitoring serum ferritin levels as well as iron overload [50]. Therefore, based on the stated mechanism, the increase in iron absorption from the digestive system and its effect on the liver causes an increase in ferritin production, and an increase in ferritin indicates an increase in iron load in the liver.

5. Conclusion

Our study showed that the frequency of blood transfusion in thalassemia patients has no effect on their liver function based on liver enzymes. Also, we found a relatively considerable correlation between serum ferritin and AST serum level. It seems that serum ferritin levels of more than 1625 mg/dL can be used as a predictor of liver damage in thalassemia patients with the highest accuracy.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

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

Authors' contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

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