

Original Article

# Investigation of non-invasive indicators of liver fibrosis in thalassemia major patients



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## ABSTRACT

Although liver biopsy is a gold standard for evaluating liver fibrosis, due to the invasive nature of the biopsy and complications related to it in thalassemia major patients, it is important to use new, valid and non-invasive methods to estimate the stage of liver fibrosis. Therefore, this study aimed to evaluate the status of non-invasive liver parameters such as FIB-4, APRI, and AAR in thalassemia major patients. The present descriptive-analytical study was conducted in 2019 on patients with thalassemia major. In this study, 140 thalassemia patients were evaluated for demographic findings, liver enzymes and non-invasive indicators of liver fibrosis. Also, underlying diseases such as diabetes, ischemic heart disease and other cases were extracted from patients' medical records. Finally, the data were entered into SPSS V20 software and evaluated. In the present study, 38.6% of the patients were male and the mean age of the patients was  $18.47 \pm 8.21$  years with an age range of 1 to 37 years. Evidence from the present study indicated that patients with thalassemia who had an abnormal liver echo had a significantly higher abnormal APRI index that was consistent with an abnormal liver echo ( $P = 0.019$ ). However, these items are not applicable for AAR and FIB-4 indicators ( $P > 0.05$ ). The correlation coefficient of APRI and AAR indices with ALT, AST and ferritin was relatively high and was statistically significant ( $P < 0.05$ ). Therefore, it can be concluded that these enzymes are well associated with changes in these indices, while there was no significant correlation between the ALKP enzyme and the above indicators. The evidence of the present study showed that non-invasive tests for liver fibrosis including APRI and AAR can have a suitable substitute in assessing the progression of liver fibrosis in thalassemia patients.

## 1. Introduction

Thalassemia is an autosomal recessive disease that is caused by various mutations of the beta-globin gene and leads to a decrease in the production of the beta-globin chain (B+ thalassemia) or its absence (B0 thalassemia) and is mainly due to point mutations in the beta-globin gene [1]. The prevalence of beta-thalassemia in Iran is very high so it can be

considered an endemic disease [2]. In beta thalassemia, major multiple blood transfusions, ineffective erythropoiesis and increased gastrointestinal iron absorption lead to iron overload in the body. Because the human body does lack a mechanism to excrete excess iron, hemosiderosis is inevitable. Iron accumulates unintentionally in various tissues such as the liver, heart and endocrine glands

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and leads to the formation of free radicals, fibrosis and body disorders. The liver is the first site of iron deposition, which leads to chronic hepatocellular damage, fibrotic changes and finally cirrhosis [2-6].

In thalassemias that are dependent on blood transfusion, liver fibrosis directly depends on the patient's age, number of blood units transfused, and liver iron concentration [7]. In fact, Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases [8]. To diagnose liver fibrosis, a patient's biopsy test is used; Considering that this method is an invasive and painful method for the patient, it has high costs and in addition, only some liver parenchymal tissues are extracted for pathological analysis, so liver biopsy cannot predict the severity of fibrosis of the whole liver [9, 10]. For these reasons, many non-invasive diagnostic methods have been proposed today. These methods are widely divided into two main branches, direct and indirect. In the indirect method, routine laboratory tests are used that do not directly examine the metabolism of the extracellular matrix. In a direct way, the components involved in the molecular pathogenesis of fibrogenesis and fibrinolysis are investigated, which reflects the metabolism of the liver extracellular matrix [11]. These biomarkers are Extracellular regeneration, enzymes involved in matrix degradation and collagen synthesis.

These markers are useful for predicting liver cirrhosis but have limited accuracy in diagnosing fibrosis [12]. Non-invasive APRI, FIB-4, and AAR tests with high diagnostic values can be used to diagnose fibrosis [13]. The APRI2 test is an index for determining the AST to platelets ratio and has been introduced as a suitable tool for measuring all types of fibrosis such as allograft fibrosis after transplantation and non-alcoholic fatty liver fibrosis [14-16]. The 4-FIB test also has the highest diagnostic value of evaluating fibrosis factor 4 even in advanced cases [17] and has the ability to check intermediate stages of fibrosis (15); This test has also provided good results regarding hepatitis fibrosis, including B and C (18). AAR3 test is also one of the

valid tests for evaluating liver fibrosis, which has been used as one of the differential diagnosis tools for hepatitis B [13]. Finally, the diagnostic power of three non-invasive tests from weak to moderate is ranked as follows: 1). The APRI2 test is an index that evaluates the AST to platelets ratio and has been introduced as a suitable tool for measuring all types of fibrosis, such as allograft fibrosis after transplantation and non-alcoholic fatty liver fibrosis [14-16].

The 4-FIB test also has the highest diagnostic value by evaluating fibrosis factor 4 even in advanced cases [17] and has the ability to check intermediate stages of fibrosis [15]; This test also has good results regarding hepatitis fibrosis, including B and C [18]. AAR3 test is also one of the valid tests for assessing liver fibrosis, which has been used as a differential diagnosis tool for hepatitis B [13]. Finally, the diagnostic power of these three non-invasive tests from weak to medium is ranked as follows: 1 (FIB-4), 2 AAR 3 APRI [19]. According to the cases mentioned in this study, non-invasive indicators of liver fibrosis in thalassemia major patients are examined.

## 2. Materials and Methods

This was a descriptive-analytical study. A total number of 140 beta-thalassemia majors in 2018-2019 referred to the Zabol Thalassemia Center with the following characteristics were examined.

### 2.1. Inclusion criteria

Thalassemia major patients

### 2.2. Exclusion criteria

Patients who have liver fibrosis due to other factors such as alcohol consumption, autoimmune hepatitis, excessive iron consumption, non-alcoholic fatty liver and bile duct obstruction. The level of desired liver enzymes using research and laboratory kits was measured and recorded.

### 2.1. Data analysis and description method

In order to compare the frequency of abnormal non-invasive indicators of APRI, FIB-4, and AAR in different groups of thalassemia major patients, a chi-square test

was used. The correlation between these indicators and liver enzymes was evaluated through a correlation test and using SPSS version 20 statistical software.

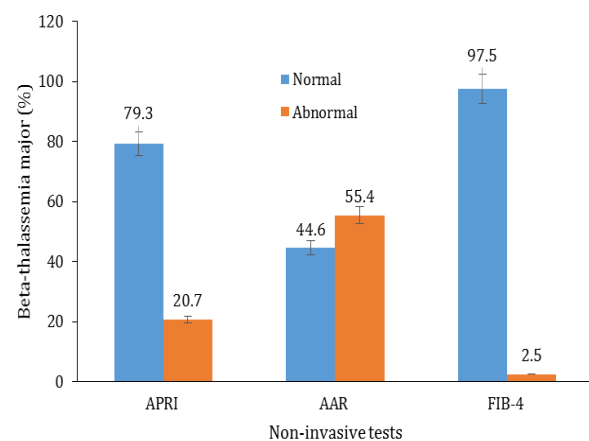
### 3. Results

The mean age of all studied populations was  $18.47 \pm 8.21$  years with an age range of 1 to 37 years. Also, the average body mass index of the participants was  $18.01 \pm 3.29$ . The lowest and highest body mass index were 12.40 and 26.40, respectively. In the present study, 54 patients (38.6%) were male and the rest were female. The average of ALT, AST and ALK P enzymes in the participants of this study was 46.41, 50.29 and 492.16 respectively. In the present study, only 5 patients (3.6%) were positive for HCV antibody, and the prevalence of diabetes, ischemic heart disease, and splenectomy was 4.3%, 37.9%, and 29.3%, respectively. In the present study, it was shown that 44 patients (31.4%) had larger liver dimensions than normal and 24 patients (17.1%) had abnormal liver echo. As shown, the APRI index in the studied patients had a mean of 0.61 and a standard deviation of 1.17.

The lowest and highest index in patients were 0.08 and 9.10, respectively. The AAR index in the studied patients had a mean of 1.2 and a standard deviation of 0.68. The lowest and highest index in patients were 0.20 and 5.10, respectively. The FIB-4 index in the studied patients had a mean of 0.72 and a standard deviation of 2.24. The lowest and highest index in patients were 0.04 and 24.30, respectively. Also, the coefficient of variation in the FIB-4 and AAR index was the highest and the lowest respectively; That is, the FIB-4 and AAR had the highest and lowest dispersion respectively (figure 1). 20.7% of the participants had an abnormal APRI index, while 79.3% of the patients had a normal index. It was found that only 44.6% of patients had normal values of AAR index and 55.4% had an abnormal AAR index (figure 1).

In this study, it was found that only 2.5% of thalassemia patients had abnormal values of FIB-4 index. The comparison of liver fibrosis indices in the two sexes shows that the frequency of abnormal APRI index in females and males was 7.22% and 4.17% respectively.

The frequency difference between the two sexes was not statistically significant ( $p=0.487$ ). Therefore, it can be concluded that the diagnostic value of this index is the same in both sexes. FIB-4 and AAR indices did not have significant statistical differences in both sexes. A comparison of liver fibrosis indices in patients with normal and abnormal liver echo shows that the frequency of abnormal APRI index was 16.8% in people with normal liver echo and 40% in people with abnormal liver echo. A comparison of liver fibrosis indices in patients with normal and abnormal liver echo shows that the frequency of the abnormal APRI index was 16.8% in people with normal liver echo and 40% in people with abnormal liver echo. The average difference between the two groups was statistically significant ( $p=0.019$ ). Therefore, it can be concluded that this index is consistent with abnormal liver echo. However, FIB-4 and AAR indices had no statistically significant relationship with liver echo results (Table 1).



**Fig. 1.** The condition of the studied patients based on the APRI, AAR, and FIB-4 index

**Table 1.** Comparison of the average indicators of liver fibrosis in patients with normal and abnormal liver echos

Hepatic indices	Liver echo		P value
	Normal	Abnormal	
<b>Abnormal APRI</b>	17(16.8%)	8 (40%)	0.019
<b>Abnormal FIB-4</b>	2 (2%)	1 (5%)	0.427
<b>Abnormal AAR</b>	55(54.5%)	12 (60%)	0.649

A comparison of the average indices of liver fibrosis in patients with normal and abnormal liver dimensions shows that the frequency of abnormal APRI index in people with normal and abnormal was 19% and 25%

respectively. The difference between the two groups was not statistically significant ( $p=0.480$ ). Therefore, it can be concluded that this index has a similar relationship with abnormal and normal liver size. Other indices also had no significant relationship with the results of liver size ( $P>0.05$ ).

The correlation of liver indices with liver enzymes and serum ferritin shows that the average ALT enzyme in patients with normal APRI index and abnormal was 88.36 and 20.109 respectively, which shows that in people with abnormal APRI, the level of this enzyme is high. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes. (Table 2). The average AST enzyme in patients with normal and abnormal APRI index was 60.38 and 76.87 respectively, which shows that the level of this enzyme is high. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes.

**Table 2.** Correlation of liver indices with liver enzymes and serum ferritin

Variable	Non-invasive tests	Spearman correlation coefficient	P value
ALT	APRI	0.62	0.000
	AAR	0.68	0.000
	FIB-4	0.20	0.024
AST	APRI	0.69	0.000
	AAR	0.33	0.000
	FIB-4	0.26	0.003
ALP	APRI	0.024	0.796
	AAR	0.083	0.368
	FIB-4	0.12	0.179
Ferritin	APRI	0.45*	0.000
	AAR	0.33	0.000
	FIB-4	0.36	0.000

The comparison of the average liver enzymes in thalassemia patients with normal and abnormal liver fibrosis indices shows that the average ALT enzyme in patients with normal and abnormal APRI index was 36.88 and 109.20 respectively, which shows that in people with abnormal APRI, the level of this enzyme is high. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes. (Table 3).

**Table 3.** Comparison of average liver enzymes in thalassemia patients with normal and abnormal APRI index

Variables	APRI	Mean	SD	P value
ALT	Normal	36.88	30.088	0.0001
	Abnormal	109.20	65.881	
AST	Normal	38.60	23.272	0.0001
	Abnormal	87.76	46.054	
ALKP	Normal	514.68	391.449	0.873
	Abnormal	485.32	234.842	
Ferritin	Normal	3428.05	2902.043	<0.0001
	Abnormal	5373.76	2747.163	

SD: Standard deviation

The average AST enzyme in patients with normal and normal APRI index was 38.60 and 87.76 respectively, which shows that the level of this enzyme is high in people with abnormal APRI. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes. The average ALT enzyme in patients with normal and abnormal APRI index was 36.88 and 109.20 respectively, which shows that the level of this enzyme is high in people with abnormal APRI. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes.

The average AST enzyme in patients with normal and abnormal APRI index was 38.60 and 87.76 respectively, which shows that the level of this enzyme is high in people with abnormal APRI. This difference was statistically significant, which shows that the abnormal APRI index is consistent with the increase in liver enzymes. The average ALKP enzyme in patients with normal and abnormal APRI index was 514.68 and 485.32 respectively, which shows that the level of this enzyme is high in people with abnormal APRI. But this difference was not statistically significant, which shows that the abnormal APRI index is not consistent with the increase in liver enzymes.

The average serum ferritin in patients with normal and abnormal APRI index was 3428.05 and 5373.76 respectively, which shows that the level of this enzyme is high in people with abnormal APRI. This difference was statistically significant, which shows that the abnormal APRI index is consistent with increased serum ferritin levels. (Table 4)

The average ALKP enzyme in patients with normal APRI index was equal to 514.68 and in patients with abnormal APRI was equal to 485.32, which shows that the level of this enzyme is high in people with normal APRI. But this difference was not statistically significant, which shows that the abnormal APRI index is not consistent with the increase in liver enzymes. Also, the average serum ferritin in patients with normal APRI index was equal to 3428.05 and in patients with abnormal APRI was equal to 5373.76, which shows that ferritin level is high in people with abnormal APRI. This difference was statistically significant, which shows that an abnormal APRI index is consistent with increased serum ferritin level.

**Table 4.** Comparison of average liver enzymes in thalassemia patients with normal and abnormal AAR index

Variables	AAR	Mean	Standard Deviation	P value
ALT	Normal	79.28	59.524	<0.0001
	Abnormal	92.69	22.225	
AST	Normal	59.48	42.479	0.002
	Abnormal	40.12	25.654	
ALKP	Normal	517.09	258.128	0.213
	Abnormal	501.78	432.739	
Ferritin	Normal	4795.75	3497.178	0.005
	Abnormal	3051.66	2192.009	

The average of ALT enzyme in patients with normal and abnormal FIB-4 index was 51.18 and 77 respectively, which shows that the level of this enzyme is high in people with abnormal FIB-4. This difference was not statistically significant, which shows that the index of Abnormal FIB-4 is not consistent with elevated liver enzymes.

The average AST enzyme in patients with normal and abnormal FIB-4 index was 48.07 and 76 respectively, which shows that in people with abnormal FIB-4, the level of this enzyme is high. This difference was not statistically significant, which shows that the Abnormal FIB-4 index is not consistent with increased liver enzymes.

The average ALKP enzyme in patients with normal and abnormal FIB-4 index was 365.542 and 361.587 respectively, which shows that in people with normal FIB-4, the level of this enzyme is high. This difference

was not statistically significant, which shows that the Abnormal FIB-4 index is not consistent with increased liver enzymes.

The average serum ferritin in patients with normal and abnormal FIB-4 index was 3770.78 and 6161.67 respectively, which shows that in people with abnormal FIB-4, the level of this enzyme is high. This difference was not statistically significant, which shows that the Abnormal FIB-4 index is not consistent with increased serum ferritin levels. The comparison of liver fibrosis indices in patients with and with no hepatitis C is shown in Table 5.

The frequency of abnormal APRI index with positive and negative hepatitis C antibody tests was 25% and 20.5% respectively. The difference between the two groups in terms of this frequency was not statistically significant ( $p>0.99$ ). Therefore, it can be concluded that the diagnostic value of this index is the same in people with and without no hepatitis C. FIB-4 and AAR indices were not statistically significantly different in the two groups. (Table 5).

**Table 5.** Comparison of liver fibrosis indices in patients with and with no hepatitis C

Hepatic indices	HCV-Ab		P value
	Positive	Negative	
Abnormal APRI	1 (25%)	24 (20.5%)	>0.99
Abnormal FIB-4	1 (25%)	66 (56.4%)	0.323
Abnormal AAR	0	3 (2.6%)	>0.99

#### 4. Discussion

Although liver biopsy is a gold standard for evaluating liver fibrosis, due to the invasive nature of the biopsy and complications related to it in thalassemia major patients, it is important to use new, valid and non-invasive methods to estimate the stage of liver fibrosis. Various indexes and indicators such as FIB-4, APRI, AAR and fibro test have been evaluated and compared with liver biopsy with different degrees of accuracy [20-23]. However, in general, these indicators are considered less [24]. Therefore, this study aims to evaluate the non-invasive liver indices in thalassemia major patients.

The evidence of the present study indicated that thalassemia patients who had an abnormal liver echo significantly had a



higher abnormal APRI index so this index was consistent with an abnormal liver echo. However, these items are not applicable to AAR and FIB-4 indicators. The correlation coefficient of APRI and AAR indices with ALT and AST enzymes was relatively high and statistically significant. Also, the comparison of liver enzymes and ferritin in people with normal and abnormal non-invasive indices showed that APRI and AAR indices are more consistent with increased liver enzymes, especially AST, ALT and serum ferritin. Therefore, it can be concluded that these enzymes have a favorable relationship with the changes of the mentioned indicators, while no significant relationship between the ALKP enzyme and the above indicators was observed [25-28]. Also, in this study, we observed that these non-aggressive indicators were similar in both sexes, which indicates that their value is probably not related to gender. On the other hand, people with abnormal liver echo only had a higher abnormal APRI; these cases show that this indicator was more related to liver involvement than other non-invasive indicators. On the other hand, people with and without no hepatitis C had the same findings in terms of these indicators.

These findings are not consistent with the results of other studies in this field. By evaluating 76 thalassemia patients with chronic hepatitis, Postchi and colleagues [29] showed that FIB-4 and APRI indices were highly accurate for evaluating liver fibrosis in thalassemia patients with chronic hepatitis C. It has also reported [30] that young patients with thalassemia and chronic hepatitis C have a high probability of suffering from liver fibrosis or cirrhosis. In this context, fibroscan, fibrotest and other non-invasive liver tests can be reliable methods to evaluate liver fibrosis. Also, in a study [15], APRI and FIB-4 indices were investigated for the non-invasive evaluation of liver fibrosis in patients with non-alcoholic fatty liver disease. The results of this study showed that these indicators are a suitable tool for evaluating fibrosis in patients with non-alcoholic fatty liver, even in advanced stages. The FIB-4 index has a better

performance in the intermediate stages of fibrosis. In a study [17], the FIB-4 index showed the highest diagnostic accuracy in the evaluation of advanced fibrosis of non-alcoholic fatty liver. Contrary to these results, in our study, FIB-4 index did not show a favorable correlation with liver involvement.

In a study it has examined [14], indices such as metalloprotease inhibitor 1 and APRI as non-invasive biomarkers of allograft fibrosis after liver transplantation in children. These researchers showed that these indicators are well able to predict the process of liver allograft fibrosis and can be used as reliable supplementary indicators. However, they cannot be a good substitute for biopsy after liver transplantation in children. In fact, transfusion-dependent thalassemia major patients often suffer from liver fibrosis, the cause of which is related to iron overload and chronic hepatitis C. Hyaluronic acid (HA) plays a prominent role in the pathogenesis of liver fibrosis. Evidence has shown that the increase in hyaluronic acid concentration is due to the increase in synthesis by inflammatory cells and hepatic stellate cells and the destruction of sinus endothelial cells [31-35]. The evidence indicates that non-invasive tests of liver fibrosis, including APRI, AAR and FIB-4 indices, can have a suitable substitute in evaluating the process and progress of liver fibrosis in thalassemia patients; however, their sensitivity and accuracy are lower than liver biopsy. One of the limitations of our study was that liver fibrosis patients were not examined for biopsy results, so it is not possible to make an accurate comparison between non-invasive indicators in patients with and without no liver fibrosis.

## 5. Conclusion

The findings of the present study showed that although liver biopsy is a gold standard for evaluating liver fibrosis, due to the invasive nature of biopsy and complications related to it in thalassemia major patients, it is important to use new, valid and non-invasive methods to estimate the stage of liver fibrosis. Non-invasive tests of liver fibrosis, including APRI and AAR indices, can have a suitable

substitute in evaluating liver fibrosis in thalassemia major patients.

### Conflict of Interest

The authors hereby declare that they have no conflict of interest.

### Author's contributions

All authors equally participated in designing experiment analysis and interpretation of data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

No human or animals were used in the present research.

### Consent for publications

All authors have read and approved the final manuscript for publication.

### Availability of data and material

The authors have embedded all data in the manuscript.

### Informed Consent

The authors declare not used any patients in this research.

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