# Screening of liver disease in thalassemic children admitted in Assiut University Hospital

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**Background**
Thalassemia is the most common hereditary disorder. Worldwide, ~7% of the population have hemoglobinopathy. In Egypt, it represents a significant public health concern. Liver disease is accelerated by iron overload, which leads to more inflammation and fibrosis, in addition to adverse effects of iron chelating agents. Iron overload is usually unavoidable in beta-thalassemia, particularly with less intensive chelation treatment. The ineffective erythropoiesis causes higher intestinal absorption, which results in chronic iron overload.

**Aim**
To evaluate the liver status in transfusion-dependent children with thalassemia major at Assiut University Children Hospital.

**Patients and methods**
A total of 100 patients with thalassemia major on regular blood transfusion were evaluated clinically and through laboratory investigations including liver function, serum ferritin, viral hepatitis markers, hepatomegaly, liver cirrhosis, liver fibrosis, and splenomegaly.

**Results**
This descriptive cross-sectional study included 100 patients with thalassemia major, and 64% of them received chelation therapy. Overall, 12% of the patients were positive hepatitis C virus (HCV) antibody. There was a strong correlation between serum ferritin and alanine aminotransferase and aspartate aminotransferase. Patients with positive HCV antibody had higher levels of alanine aminotransferase and aspartate aminotransferase. In addition, there are high levels of serum ferritin in patients with HCV-positive antibodies.

**Conclusion**
Hepatic affection is common in thalassemic patients, which is more profound in patients with iron overload and those with chronic hepatitis C infection. Screening of liver affection using abdominal sonography, liver enzymes, serum ferritin, and virology screening seems to be essential for management of patients with thalassemia major.

**Keywords:**
beta-thalassemia, Egyptian children, hepatitis markers, iron overload, liver enzymes

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## Introduction

Thalassemia is the most common hereditary disorder; ~7% of the population have hemoglobinopathy [1]. In Egypt, it represents a significant public health concern [2,3].

The patients with beta-thalassemia need life-long transfusion therapy to maintain normal growth and inhibition of ineffective erythropoiesis [4]. Iron overload is usually unavoidable, particularly with less intensive chelation treatment [5]. In addition, ineffective erythropoiesis causes higher intestinal absorption, resulting in chronic of iron overload [6].

The frequent blood transfusion in patients with thalassemia makes these patients vulnerable to transfusion-associated infection, especially hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection, which cause chronic infection. The prevalence of transfusion-transmitted infection decreased owing to the national blood screening in 1993 and recently owing to introduction of nucleic acid testing [7]. HCV infection among patients with B-thalassemia ranges from 11 to 69% in the eastern Mediterranean, differing according to patients' age and seroprevalence [8].

Liver disease is severe in patients with thalassemia and accelerated by iron overload, which leads to more inflammation and fibrosis [5,9,10], because the liver plays an important role in iron metabolism in the whole body [8].

Liver fibrosis may be caused by minimal hemosiderosis, so iron overload is very critical in the late stage of liver damage independently of HCV infection [11].

Patients with thalassemia who underwent bone marrow transplantation showed that HCV infection and iron overload are independent risk factors in hepatic injury [12]. HCV infection is the major cause of liver damage in patients with beta-thalassemia [13]. Gallstones are described as one of the most prevalent complications of thalassemia. Gallstone formation is mostly owing to iron deposition, followed by hemolysis and ineffective erythropoiesis, which results in gastrointestinal symptoms in patients and frequently results in a cholecystectomy [14].

Our aim is to evaluate liver affection in children with thalassemia major at Assiut University Children Hospital.

## Patients and methods

This was a descriptive cross-sectional study of patients with thalassemia major done at the Pediatric Haematology Unit, Children Hospital of Assiut University, for 6 months. The study included 100 patients with known thalassemia major (64 males and 36 females). Their ages ranged from 1.1 to 17 years, with 56% with a family history of the same disease. Patients with β-thalassemia major (transfusion-dependent) aged from 1 to 17 years old were included in the study. We excluded patients with congenital liver diseases, nontransfusion dependent thalassemic patients, and patients with thalassemia minor. History from patients was taken, including demographic data such as name, sex, age, socioeconomic status, consanguinity, family history of same disease, age of first blood transfusion, blood transfusion interval, and age starting chelation; clinical data, including pallor, presence jaundice evidence, hepatosplenomegaly, or splenectomy; sonographic data of liver size; and laboratory data, including liver function tests [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], serum ferritin level, and hepatitis markers, including hepatitis B surface antigen (HBsAg) and anti-HCV antibody.

### Ethical approval

The study was approved by ethical committee of Faculty of Medicine, Assiut University, with number of approval number 17101167, on 28/09/2016.

### Statistical analysis

Results are expressed as mean ± SD or *n* (%). Comparison between values of different parameters in the studied groups was performed using Kruskal–Wallis test, followed by Mann–Whitney test as a post-hoc test if significant results are recorded. Comparison between categorical data was performed using $\chi^2$ test. SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) (version 23 Windows) was used for data analysis. *P* value less than or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

## Results

The study included 100 patients (64 males and 36 females) with known thalassemia major. Their ages ranged from 1.1 to 17 years, with a mean ± SD of 8.54 ± 4.59 years and median (interquartile range) of 7 (5–13). Overall, 56% had a family history of the same disease (Table 1). Patients received blood transfusion regularly.

The age of first blood transfusion ranged from 2 to 36 months, with a mean of 12.46 ± 8.55 months, and blood transfusion interval every month ranged from 0.2 to 6 months, with a mean of 1.24 ± 0.96 months, with a significant decrease in blood transfusion interval with splenectomy, with *P* value of 0.013 (Tables 2 and 3).

What is the significance of classifying splenomegaly in this manner?

This clinical examination of spleen.

**Table 1 Demographic data of the studied patients**

| Age group | | *n* (%) |
|---|---|---|
| Toddlers (1-2 years) | 4 (4.0) | |
| Preschool (3-5 years) | 24 (24.0) | |
| School age (6-12 years) | 46 (46.0) | |
| Adolescent (13-16 years) | 22 (22.0) | |
| More than 16 years | 4 (4.0) | |
| Range | Mean±SD | Median (interquartile range) |
| 1.1-17 | 8.54±4.59 | 7 (5-13) |
| Range | Mean±SD | Median (interquartile range) |
| 1.1-17 | 8.54±4.59 | 7 (5-13) |
| Sex | | *n* (%) |
| Male | 64 (64.0) | |
| Female | 36 (36.0) | |
| Family history | | *n* (%) |
| Positive | 56 (56.0) | |
| Negative | 44 (44.0) | |
| Presence of jaundice | | *n* (%) |
| No | 4 (4.0) | |
| Yes | 96 (96.0) | |
| Pallor | | *n* (%) |
| No | 0 | |
| Yes | 100 (100.0) | |
| Splenomegaly | | *n* (%) |
| Not palpable | 12 (12.0) | |
| ≤5 cm | 30 (30.0) | |
| >5≤10 cm | 8 (8.0) | |
| >10 cm | 16 (2.0) | |
| Splenectomy | 34 (34.0) | |

Why you did not mention the value of direct bilirubin (after the value of total bilirubin) which is more specific for hepatic affection?

Because the total bilirubin is mainly indirect due to hemolysis of the thalassemia.

Overall, only four patients experienced gall bladder stone, as it is one of thalassemia complications (Tables 4 and 5). Echocardiography shows that four patients have mitral regurge, whereas two were on antifailure treatment (Table 4).

Mild enlargment 2 cm above normal, moderate: 4 cm above normal, and marked: 6 cm above normal.

This is according to Radiology Department protocol for abdominal ultrasonography in children at Assiut University Hospital.

In this study, 64 patients received chelation therapy (four of them on deferiprone and 60 patients on deferasirox).

None of studied patients were positive for HBsAg, whereas 12% of the patients were positive for HCV antibody (Ab).

There is a strong positive correlation between serum ferritin and ALT and AST, with *P* values of 0.000 and 0.001, and *r* values 0.475 and 0.354 , respectively, and there is also a positive correlation between liver size and AST and ALT, with *P* values of 0.004 and 0.014 and *r* values of 0.298 and 0.254, respectively (Table 6).

Patients with positive HCV Ab had higher levels of ALT and AST, with *P* value of 0.040 and 0.042, respectively (Table 7). In addition, there are high levels of serum ferritin in patients with HCV-positive antibodies, with *P* value of 0.049.

Patients who received iron chelation therapy had a higher level of ALT compared with those not receiving chelation therapy, with *P* value of 0.032 (Table 8).

## Discussion

The aim of this study was to evaluate liver affection in children with transfusion-dependent thalassemia major at Hematology Unit in Assiut University Children Hospital and to evaluate the potentiating effect of viral hepatitis and iron overload on liver enzymes as an indicator of hepatic injury in Egyptian children with thalassemia major and to throw light on the percentage of HCV and HBV infection in studied thalassemic children. This study was conducted on 100 thalassemic patients, and 34 of them underwent splenectomy, which resulted in a significant increase in the interval of blood transfusion compared with the nonsplenectomized children ($P = 0.013$). These results are in accordance with the study of Al-Salem and Nasserulla [15] and Salama *et al.* [16]. In addition, Hubail and Morsy [17] revealed that in the splenectomized group of their patients, the total amount of blood given decreased all over the year.

Our results showed higher levels of liver enzymes in patients treated by iron chelation than those not receiving chelation therapy, but the difference was significant only in serum ALT level, with *P* value of 0.032. This finding was the same as Salama *et al.* [16], who concluded that the mean serum ferritin level was significantly higher

**Table 2 Starting age of blood transfusion and chelation therapy**

| | Range | Mean±SD | Median (interquartile range) |
|---|---|---|---|
| Age of 1st blood transfusion (months) | 2-36 | 12.46±8.55 | 10 (6-18) |
| Blood transfusion interval (months) | 0.2-6 | 1.24±0.96 | 1 (1-1) |
| Age at starting chelation (years) | 1-15 | 5.35 ± 2.87 | 5 (4-6.75) |

**Table 3 Laboratory data of studied patients**

| | Range | Normal (value) | Mean | Median |
|---|---|---|---|---|
| WBCs | 3.8-26 | 4-15×03 $mm^3$ | 9.75±4.97 | 8.75 (6.23-11.35) |
| HB | 3.4-12.3 | 11-16 g/dl | 7.18±1.88 | 7 (6-8.55) |
| Platelets | 72-990 | 140-450×$10^3$ $mm^3$ | 329.25±202.63 | 255.5 (182-467) |
| Hb-A2 | 1.3-7 | 2-3% | 3.7±1.42 | 3.45 (2.5-4.5) |
| Hb-F | 10.4-98 | 0.8-2% | 72.46±19.51 | 77.5 (66-86) |
| Hb-A | 8-86 | 95-98% | 37.83±32.98 | 21.85 (12.3-77) |
| ALT | 10-174 | Up to 41 U/l | 54.83±38.76 | 43 (22-75) |
| AST | 6-210 | Up to 37 U/l | 63.29±39.41 | 53.5 (33-75) |
| Total bilirubin | 0.1-6.8 | 0.2-1.0 mg/dl | 1.87±1.26 | 1.7 (1.2-2.2) |
| Albumin | 0.8-4.8 | 3.5-5 g/dl | 3.28±0.91 | 3.3 (3-4) |
| Serum ferritin | 65-5498 | 7-140 ng/ml | 1367.52 ± 856.22 | 1500 (700-1805) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB, Hemoglobin; WBC, white blood cell.

in thalassemic patients with elevated ALT or elevated AST ($P$ = 0.000 and 0.001, respectively). Furthermore, these findings are in agreement with other previous studies [4,16,18], which reported that abnormal ALT level is associated with higher ferritin and transferrin saturation. None of the patients included in this study were HBsAg positive. The absence of HBV infection among patients with thalassemia was also reported by Salama *et al.* [16], Ameli *et al.* [4], and Omar *et al.* [19]. HBV infection occurred in one (2%) patient from 50 thalassemic patients in the study of El Gawhary *et al.* [20], whereas in a study conducted by El-Faramawy *et al.* [21], 12% of patients were infected with HBV. There is a decrease in the prevalence of HBV infection in this study and some other studies, which indicates the efficacy of the vaccination program and the effective screening of blood and blood products. Although the prevalence of HBsAg among Egyptian children on regular transfusion decreased, it is high in some studies in several geographical areas, and this might be attributed to the high infection rates among children in these areas despite vaccination, as they might not respond adequately to vaccination or may not be absolutely immunized or may be owing to poor screening techniques in blood banks.

In this study, 12% of the patients were positive for HCV Abs which is lower compared with previous studies; for example, in a study conducted by Salama *et al.* [16], 50% of patients were positive for HCV Abs. The lower prevalence in this study may be owing to the relatively young age of studied patients and also the effective screening of blood and blood products. Li *et al.* [22] reported that 8% of their studied patients were HCV Abs positive, and also the study of Omar *et al.* [19] reported that 51.7% of their patients were HCV Abs positive. In addition, Din *et al.* [23] revealed that in their study, 49% of thalassemic patients were positive for anti-HCV Abs. Furthermore, Hussein [24] reported that in their study, 24% of Egyptian thalassemic children who received frequent transfusions were positive for HCV Abs.

**Table 4 Sonographic data of studied cases**

| Biliary problems (gallstones) | *n* (%) |
|---|---|
| No | 96 (96) |
| Gallstones | 4 (4.0) |
| Echocardiographic changes | |
| Heart failure | 2 (2.0) |
| Mitral regurge | 4 (4.0) |

In this study, HCV Ab-positive patients had higher mean serum ferritin, AST, and ALT level than the negative patients ($P$ = 0.049, 0.040, and 0.042, respectively). This is in agreement with the results of Salama *et al.* [16], and the findings of Ocak *et al.* [25], which revealed that the patients who were anti-HCV positive had a significantly higher peak serum ALT level than anti-HCV-negative patients. Ameli *et al.* [4] found that serum iron was significantly higher in anti-HCV-positive patients compared with the negative group. Moreover, Omar *et al.* [19] stated that those with HCV Ab positivity had significantly higher serum ferritin and higher liver transaminase levels.

The results of this work showed that the level of serum ALT was highly significantly correlated with the age of the patients ($P$ = 0.032), which was in agreement with the result of Salama *et al.* [16].

## Conclusion

Hepatic affection is common in thalassemic patients, which more profound in patients with iron overload and those with chronic hepatitis C infection. Screening of liver affection using abdominal sonography, liver enzymes, serum ferritin, and virology screening seems to be essential for management of patients with thalassemia major.

### Study limitation

This study has many limitations such as evaluation of hepatic iron overload by MRI. as well as their limitations, using fibroscan for evaluation of the degree of hepatic fibrosis and liver biopsy. This is greatly attributed to financial issues.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Table 5 Liver span by abdominal ultrasonography**

| | Range | Mean±SD | Median (interquartile range) |
|---|---|---|---|
| Liver span | 10.5-20 | 15.15±2.73 | 15.0 (13.5-17.5) |
| Average | 10 | | |
| Mild hepatomegaly | 42 | | |
| Moderate hepatomegaly | 44 | | |
| Marked hepatomegaly | 4 | | |

**Table 6 Correlation between liver size, serum ferritin, alanine aminotransferase, and aspartate aminotransferase**

| | Liver size | Serum ferritin | AST | ALT |
|---|---|---|---|---|
| Liver size | | | | |
| *r* | 1 | | | |
| *P* | | | | |
| Serum ferritin | | | | |
| *r* | 0.105 | 1 | | |
| *P* | 0.299 | | | |
| AST | | | | |
| *r* | 0.298 | 0.354 | 1 | |
| *P* | 0.004 | 0.001 | | |
| ALT | | | | |
| *r* | 0.254 | 0.475 | 0.824 | 1 |
| *P* | 0.014 | 0.000 | 0.000 | |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Table 7 Comparison between liver function (alanine aminotransferase and aspartate aminotransferase) and serum ferritin with hepatitis C virus antibody**

| | Hepatitis C virus antibody | | *P* |
|---|---|---|---|
| | Positive (*n*=12) | Negative (*n*=88) | |
| | Mean±SD | Mean±SD | |
| ALT | 82.16±5.8 | 53.89±46.84 | 0.040 |
| AST | 86.09±30.09 | 59.64±40.9 | 0.042 |
| Serum ferritin | 1595.1 ± 475.9 | 1150.8 ± 750.6 | 0.049 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Table 8 Comparison between liver function (alanine aminotransferase and aspartate aminotransferase) and serum ferritin regarding chelation therapy**

| | Administration of chelation therapy | | *P* |
|---|---|---|---|
| | On chelation (*n*=64) | Not on chelation (*n*=36) | |
| | Mean±SD | Mean±SD | |
| ALT | 63±48.95 | 41.94±33.24 | 0.032 |
| AST | 67.38±43.89 | 54.22±32.32 | 0.139 |
| Serum ferritin | 1010.5 ± 630.68 | 1568.34 ± 904.01 | 0.001 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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### Conflicts of interest

There are no conflicts of interest.

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