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Original article

Serum Levels of Ischemia Modified Albumin in Children with *β*-Thalassemia Major

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Abstract

Background and aim: Thalassemia is a prevalent genetic disorder in Egypt. The objective of this study was to assess the serum ischemia modified albumin (IMA) level in children diagnosed with β-thalassemia major. **Methods:** This case-control study included 60 children with thalassemia major, diagnosed with hemoglobin electrophoresis, and on regular blood transfusion and 30 healthy children as a control group. Ischemia modified albumin (IMA) evaluation using an ELISA kit was one of many laboratory investigations conducted on each child after a comprehensive history taking and physical examination. **Result:** The results showed that there was a statistically significant difference in IMA between the groups studied. It was higher in the Beta Thalassemia patient group compared to the control group, and it was even higher in β-thalassemic patients who had undergone splenectomy. IMA was positively correlated with the mean corpuscular hemoglobin, hematocrit, and ferritin, and negatively correlated with the Hb level. When multivariate logistic regression was used to predict a significant increase in IMA, ferritin and splenectomy were both found to be statistically significant factors. **Conclusion:** Follow-up evaluations of β-thalassemic patients may benefit from the use of ischemia modified albumin as a biomarker for the early diagnosis of consequences.

Keywords: Ischemia Modified Albumin; IMA; Children; *β*-Thalassemia Major

Introduction

Thalassemia refers to a collection of diseases characterized by abnormally low hemoglobin levels. There are several subtypes within the two primary forms of thalassemia, alpha and beta. Many people have beta thalassemia minor, which is another name for beta thalassemia trait. The American physician Thomas Cooley did not publish the initial description of beta thalassemia major until 1925. One extremely dangerous blood disorder is beta thalassemia major, which goes by several names as Cooley's anemia. Older terms such as thalassemia minor, intermedia, and major have been replaced by newer ones for thalassemia, such as transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT) (1)**.** Beta thalassemia major is characterized by anemia and transfusion requirements, the hallmark symptoms of the condition. Patients who begin treatment early and consistently rarely have the classic clinical picture of the condition (2).Excessive iron buildup in various organs caused by chronic blood transfusion therapy was linked to high rates of early mortality. Iron chelators, particularly the oral one, have increased survival rates in the past ten years (3).

As a result of oxidative stress, reactive oxygen species (ROS) production, and acidosis, albumin properties undergo certain changes during ischemic attacks (4). Oxidative stress alters the biochemistry and structure of a protein, forming ischemia-modified albumin (IMA). The affinity of the NTS for transition metals, particularly cobalt, is reduced due to this modification. The NTS of human serum albumin (HSA) is Asp1-Ala2-His3-Lys4 (5).

Hypothyroidism, hyperthyroidism, diabetes mellitus, cerebrovascular accidents, renal failure, myocardial infarction, and cerebrovascular accidents are among the many diseases linked to ischemia and oxidative stress that have IMA as a potential early biomarker (6)**.**

Patients suffering from β-thalassemia major experience iron overload due to the need for ongoing blood transfusions. Iron excess and iron-induced oxidative stress are recognized in thalassemia major patients. Oxidative stress, reactive oxygen species (ROS) production, and oxidation reduction active iron forms are manifestations experienced by patients with β-thalassemia major. Thus, it's plausible that such circumstances lead to a change in the structure of human serum albumin that permits an overabundance of IMA (7).

Serum ischemia modified albumin (IMA) levels in children with β-thalassemia major were the focus of the study.

Subjects and methods

This case-control study was conducted. The patients were collected from the Hematology Unit, Department of Pediatrics, Benha University Hospitals, while the laboratory investigations were done in the Clinical & Chemical Pathology Department- Benha

University Hospitals from August 2023 to June 2024.

Approval Code: MS 27-7-2023

Sample size:

We calculated the least required sample size at 0.05 alpha error, power of 0.80 and prevalence of 2.4%. The least number was 36 patients allowing non-responder. Drop out or missed data and to increase validity of the study result, the sample size was adjusted and increased to 60 patients.

Sixty children, who had beta thalassemia major were part of the study, while thirty age and sex matched apparently healthy children served as a control group. All the parents provided their informed consent. Number MS 27-7-2023 indicates that the protocol has been approved by the institutional ethical committee.

Participants were male and female children ranging in age from 1 to 16 years. The patients had thalassemia major, diagnosed with hemoglobin electrophoresis, and received blood transfusions on a regular basis. We did not include patients who had another chronic hemolytic anemia or other chronic diseases such as diabetes mellitus, kidney disease, or cardiovascular disease. A thorough medical history, physical examination, and battery laboratory tests were done to each patient.

Collection of Blood Samples

For each child in this study 6 ml of venous blood were drawn under strict aseptic conditions prior to their routine blood transfusion for:

1. CBC: EDTA was added to all samples that were taken immediately. Hemoglobin, platelet, total and differential white blood cell, and red blood cell (RBC) counts were measured using the Sysmex KX-21N (Sysmex Corporation, New York, USA).

2. Liver and kidney function tests: serum was collected, using INDIKO- thermos and DiAlab-thermo to detect serums level of AST, ALT, Urea and Creatinine.

3. Serum ferritin level was measured with an immunoassay technique using Master T Hospitex Diagnostics by biosystem kits.

4. Ischemia Modified Albumin; using Ischemia Modified Albumin ELISA Kit: (ELISA Kits purchased from Shanghai Sunred bio, Company, Ltd., china).

Statistical methods

Our data was analyzed using IBM SPSS statistics (V. 26.0, IBM Corp., USA, 2019). The quantitative parametric measurements were presented as Mean ± SD, whereas the classified data were presented as number and %. A battery of tests was conducted: Qualitative metrics, such as number and percentage, as well as quantitative metrics, such as number of instances, mean, standard deviation, and range (minimum to

maximum). Quantitative factors were analyzed for normally distributed data comparing the two groups using the student t-test. For the Mann-Whitney Applying the U-test to compare two sets of data that do not follow a normal distribution. An analysis of normally distributed quantitative data comparing two groups using the post hoc test. - Qualitative data was analyzed between groups using the c2-test. Analyzing data: Using a paired t-test, we compared two dependent groups' parametric data. We estimated the correlation between each pair of variables using Pearson's correlation coefficient. We estimated the area under the curve (AUC), sensitivity, specificity, positive predictive value (NPV), and negative predictive value (NPV) by examining the receiver operating characteristic curve. With a p-value of less than 0.05, statistical significance was established.

Results

There was no statistically significant difference between the beta thalassemia patients and the control group in terms of age, sex, consanguinity, or family history in this research, which included 60 children with thalassemia. Their mean age was 10.56±4.1 years**, table 1**

The mean onset of the disease was 13±0.7 (6-24) months, the mean duration of the disease was 6.41±4.1 (1.41-14.41) years. The percentage of mongoloid features was 65%, and the most common sign was hepatomegaly (100%). About 43.3% of patients needed a blood transfusion every 4 weeks, 36.7% need blood transfusion every 3 weeks and 20% of patients need blood transfusion every 2 weeks. The mean age of start of blood transfusion was 4.7±0.87 years and 41.7% of the patients took deferasirox chelation therapy, 26.7% took deferoxamine chelation therapy, 31.6%of patients took deferiprone chelation therapy. The mean age of start of chelation therapy was 2.8±0.99-year, **table 2**.

Hematocrit value, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCH), and hemoglobin levels were all significantly lower in the thalassemic anemia group than in the control group. Patients with thalassemic anemia have elevated serum ferritin levels when compared with the controls. When looking at white blood cell, platelet, alanine aminotransferase, urea, and creatinine levels, there was no statistically significant break, **table 3**.

There was statistically significant difference between the studied groups regarding ischemia modified albumin, as it was higher in beta thalassemia patients (range 50.36- 543.15 ng/ml and mean 114.74±111.02 ng/ml) than in the control group (range 30.4- 64.2 ng/ml, mean 47.5±10.58 ng/ml) ($p<0.001$), **figure 1**. There was statistically significant difference between the patients with splenectomy (mean 179.4±46.6 ng/ml) and without splenectomy (mean 110.7±45.9 ng/ml) regarding IMA, as it was higher in the patients' group with splenectomy, **figure 2**.

The relationship between ischemia-modified albumin and various iron chelating agents revealed strong positive correlations. The mean corpuscular

hemoglobin, ferritin, hematocrit, and mean corpuscular volume positively correlated with IMA, whereas Hb was negatively correlated, **table 4**.

ROC analysis for ischemia modified albumin for prediction of complications of beta-thalassemia showed that, at a cutoff point of more than 67.14 ng/ml, IMA had sensitivity of 85% and specificity of 93% with high significance for prediction of beta-thalassemia complications, **figure 3**.

Using multivariate logistic regression, both ferritin and splenectomy were statistically significant factors for prediction of significant ischemia modified albumin (P-values 0.001 and 0.003 respectively).

Table (1): Demographic data of the groups studied.

Demographic data	Group A Patients group (N=60)	Group B Control group (N=30)	P value
Age (years) Mean± SD	10.56±4.1	10.73±3.9	**0.87**
Sex			
Male	35 (58.3%)	17 (56.7%)	**0.86**
Female	25 (41.7%)	13 (43.3%)	
Consanguinity			
Yes	8 (13.3%)	3 (10%)	**0.64**
No	52 (86.7%)	27 (90%)	
Family history of thalassemia			
Yes	9 (15%)	2 (6.7%)	**0.25**
No	**51 (85%)**	**28 (93.3%)**	

Table (2): Clinical characteristics of thalassemic patients

Clinical characteristics		N=60	
Onset of disease (months) Mean± SD (range)		13±0.7 (6-24)	
Duration of disease (years) Mean± SD (range)		6.41±4.1 (1.41-14.41)	
Mongoloid Features	**Yes**	39	65%
	No	21	35%
Hepatomegaly	**Yes**	60	100%
	No	0	0%
Spleen Splenomegaly	**Yes**	35	58.3%
	No	22	36.7%
Splenectomy	**Yes**	3	5%
Duration of need Blood Transfusion (Mean±SD = 17.5±6.92 days)	**2 weeks**	12	20%
	3 weeks	22	36.7%
	4 weeks	26	43.3%
Age of starting blood transfusion		4.7±0.87 year	
Types of chelation therapy			
Exjade® (Deferasirox)		25 (41.7%)	
Desferal® (Deferoxamine)		16 (26.7%)	
Ferriprox ® (Deferiprone)		19 (31.6%)	
Age of starting chelation therapy, Mean±SD.		2.8±0.99 year	

Table (3): Laboratory investigations of the studied groups.

Laboratory investigations		Group A Patients group (N=60)	Group B Control group (N=30)	P value
Hb (g/dl)	Median (min-max)	8.7 (7.4-11.3)	12.5 (8-16)	**<0.001**
	Mean± SD	8.79±0.62	12.14±1.79	
Hematocrit (%)	Median (min-max)	27.3 (22-44.1)	29 (19-40)	**<0.001**
	Mean± SD	10.3±5.1	28.4±4.1	
MCV (fL)	Median (min-max)	61.5 (50.6-70.6)	83 (78-88)	**<0.001**
	Mean± SD	67.12 ± 4.9	83.1±2.3	
MCH (pg)	Median (min-max)	26.9 (٢٠.٥-٢٩.٤)	28 (25-31)	**<0.001**
	Mean± SD	24.51± 2.26	27.3± 1.5	
PLT (10^3/uL)	Median (min-max)	313 (171-٧20)	355 (57-756)	0.054
	Mean± SD	292.4± 98.6	349.7±145	
WBC (10^3/uL)	Median (min-max)	6.72 (3.6-16.2)	9.5 (2.5-19)	0.69
	Mean± SD	8.6±4.8	9.1±3.78	
ALT (ul /L)	Median (min-max)	29 (14-278)	24.65 (2-36)	0.18
	Mean± SD	36.41±34.68	25.9±11.4	
AST (ul /L)	Median (min-max)	43 (23-130)	28.8 (13-35)	0.18
	Mean± SD	43.88±13.65	26.91±12.6	
Urea (mg/dl)	Median (min-max)	28 (15-47)	13.2 (9.1-17.1)	0.098
	Mean± SD	28.21±8.52	14.12±7.89	
Creatinine (mg/dl)	Median (min-max)	0.4 (0.3-0.6)	0.52 (0.1-0.9)	0.54
	Mean± SD	0.46±0.09	0.48±0.2	
Ferritin (ng/ml)	Median (min-max)	296 (238-320)	11.55 (1.8-23.5)	**<0.001**
	Mean± SD	287.53±19.42	10.3±5.1	

Hb: Hemoglobin, **MCV**: Mean corpuscular volume, **MCH**: Mean corpuscular hemoglobin, **PLT:** Platelet**, WBC**: White blood cells, **ALT**: Alanine transaminase, **AST**: Aspartate transferase

Table (4): Correlation between Ischemia Modified Albumin and (different iron chelators and laboratory investigations)

Iron chelators and laboratory investigations	Ischemia Modified Albumin		
	Mean± SD	**r coefficient**	**P value**
Age of starting chelation therapy	**2.8±0.99 years**	**0.116**	**0.376**
Exjade® (Deferasirox)	**83.9±112.06 years**	**0.1573**	**<0.001**
Desferal® (Deferoxamine)	**71.74±83.17 years**	**0.12748**	**<0.001**
Ferriprox ® (Deferiprone)	**78.8±129.4 years**	**0.1363**	**<0.001**
Hb (g/dl)		**-0.403**	**<0.001**
WBC (10^3/uL)		**0.٢٣٠**	**٠.٢١٤**
MCV (fL)		**0.٥٠٢**	**<0.001**
MCH (pg)		**0.٤٩٩**	**٠.٠٠٥**
PLT (10^3/uL)		**0.٣٠١**	**٠.٠٩**
Hematocrit (%)		**0.٤٨٦**	**٠.٠٢١**
Ferritin (ng/ml)		**0.434**	**<0.001**
AST (ul /L)		**0.03129**	**0.18**
ALT (ul /L)		**0.016734**	**0.38**
Urea (mg/dl)		**0.035705**	**0.37**
Creatinine (mg/dl)		**0.03998**	**0.54**

Hb: Hemoglobin, **MCV**: Mean corpuscular volume, **MCH**: Mean corpuscular hemoglobin, **PLT:** Platelet**,** **WBC**: White blood cells, **ALT**: Alanine transaminase, **AST**: Aspartate transferase

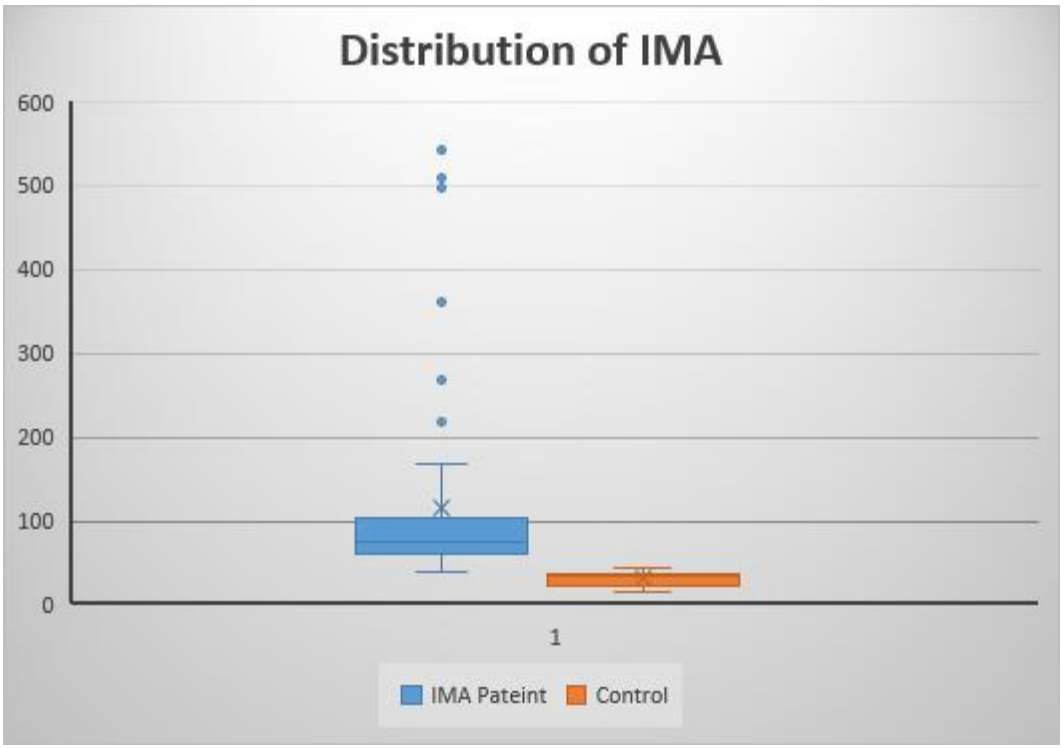

Figure 1: Distribution of IMA between the studied groups.

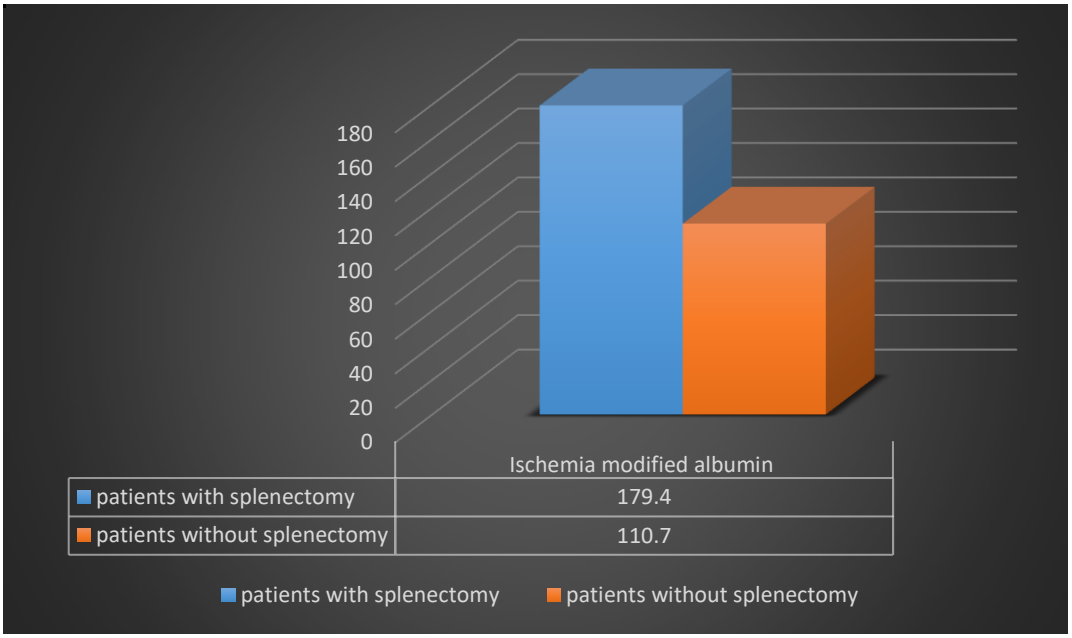

Figure 2: Comparison between IMA in patients with splenectomy and those without splenectomy in the studied group.

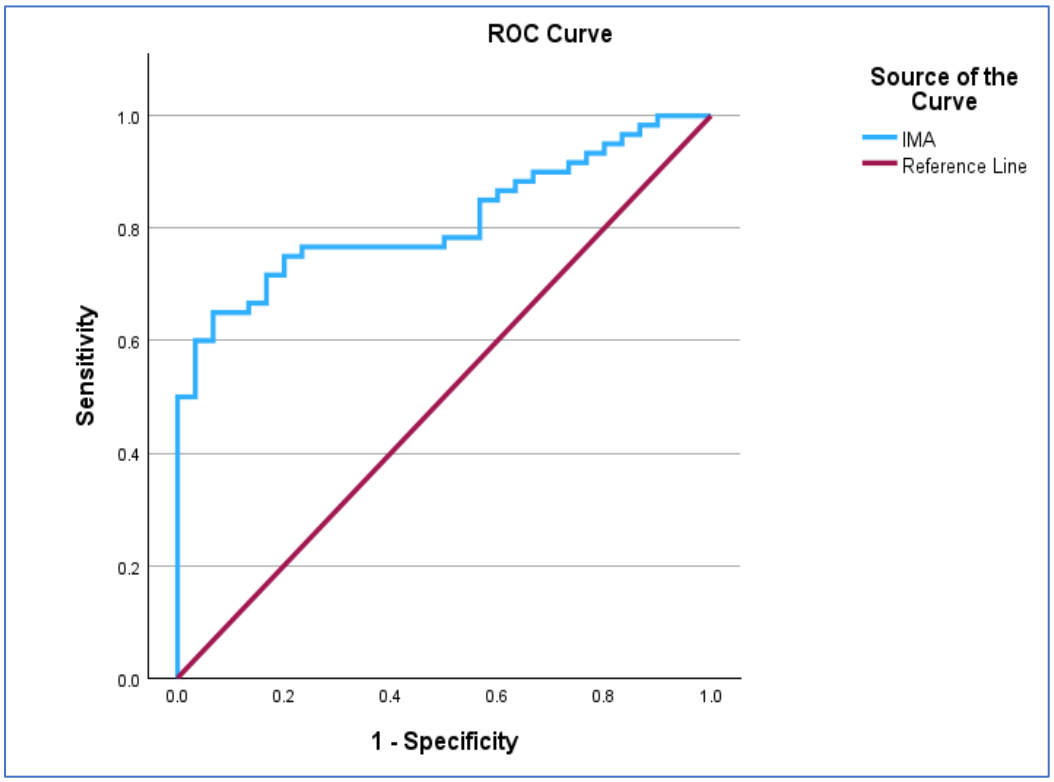

Figure 3: ROC curve of IMA for prediction of beta-thalassemia.

Discussion

Beta thalassemia syndromes are a group of haemoglobinopathies characterized by nonexistent or impaired beta globin chain production, which leads to symptoms such as hemolysis, anemia, and ineffective erythropoiesis (8). Thalassemia patients benefit significantly from chelation treatment and frequent blood transfusions in terms of both quality of life and duration of life. One major issue with prolonged blood transfusions is iron overload, which leads to an increase in free radical production and tissue peroxidative damage (9).

In reaction to free radicals, serum albumin undergoes a modification that results in ischemia modified albumin (IMA). Factors like ischemia, hypoxia, acidosis, free radicals, and free iron can produce reactive oxygen species, which can reduce the binding affinity of the N-terminus for transition metals(10).

In our study, patients with beta thalassemia had greater levels of IMA than those in the control group. Additionally, there was a statistically significant difference between the patients who underwent splenectomy and those who did not. The latter group exhibited the highest levels of IMA.

Our results run in concordance with *Moftah et al.,* (11)**.** They found that the mean IMA was 86.5 ± 13.5 ng/ml which was much higher than that of the control group (3.75 ± 1.35 ng/ml). The mean IMA in thalassemic patients with splenectomy was 97.5 ± 8.5 ng/ml

which was higher than that in the patients without splenectomy (85.6 ± 8.3 ng/ml). In the same way *Kumar et al.,* (12) reported that the mean IMA of the patients (1399.57 ng/dl) was much higher than that of the control group (377.19 ng/dl). Also, our results agreed with *Mousa et al.,* (13) who found that the mean IMA of thalassemic patients was 485.4±640.7 ng/ml which was much higher than that of the control group (43.8 ± 27.3 ng/ml). *Awadallah et al.,* (14) stated that the mean IMA levels were considerably greater in thalassemia patients compared to healthy controls.

One possible explanation for the elevated IMA level in thalassemia patients is anemia. Mild hypoxia is caused by low hemoglobin levels and altered metal-albumin binding in anemia. Low hemoglobin levels can affect both the arterial O_2 content and tissue oxygen delivery, which in turn causes an increase in IMA levels (14).

While Ischemia Modified Albumin was negatively correlated with Hb in the present study, it was positively correlated with the mean corpuscular volume, mean corpuscular hemoglobin, hematocrit value, and ferritin. Additionally, IMA was significantly correlated with the age at which chelation therapy (deferasirox, deferoxamine, and deferiprone) was initiated. All the three medications were positively correlated with IMA (r=0.1357, P-value= <0.001, r=0.12748, P-value= <0.001, and r=0.1573, P-value= <0.001, respectively). The younger the age of starting chelation treatment the lower the IMA level (r=0.116, P value= 0.376). In contrast to thalassemic patients treated with deferasirox or Deferoxamine, those given deferiprone exhibited significantly lower levels of IMA, according to our study. The reason is that deferiprone lowers blood and cellular iron levels by chelating excess iron, which in turn lowers reactive oxygen species (ROS) formation.

Our results agreed with *Kumar et al.,* (12) who stated that IMA had a positive correlation with MCV and MCH and a significantly negative correlation with Hb. There was a statistically significant positive correlation between the levels of blood ferritin and IMA. A positive correlation between IMA and Deferasirox was demonstrated (r= 0.1521, P-value= <0.001).

Also, our results were in agreement with *Moftah et al.,* (11) who discovered that IMA was positively correlated with age, sex, anthropometric measurements and chelation therapy, negatively correlated with clinical characteristics and positively correlated with serum ferritin, AST, ALT, urea and creatinine.

Our result also matched with *Adly et al.,* (15) who discovered that there was a statistically significant positive correlation between IMA levels and disease duration (r = 0.311, p = 0.045), white blood cell count (r = 0.322, p = 0.031), serum ALT (r = 0.388, p = 0.01), and AST (r = 0.382, p = 0.037). There were positive correlations between the mean levels of serum ferritin and both malondialdehyde (MDA) (r =0.503, p = 0.001) and IMA (r = 0.645, p <0.001) in patients with thalassemic disease.

In *Mousa et al.,* (13)**,** a significant decrease in IMA levels was observed in thalassemic children on DFP iron chelation therapy when compared to those who were not on chelation therapy ($P < 0.001$). Additionally, they discovered a strong positive association between serum ferritin and levels of CRP and IMA in thalassemic disease. Furthermore, in children with thalassemic disease, IMA and CRP levels were positively correlated. Similar to our results, *Akrawinthawong et al.,* (16) discovered that DFP treatment improved the oxidative stress and iron overload when administered alone. This is because too much iron can be chelated by DFP, which means less free iron in the blood and inside cells, which means less ROS can be formed. Chelation therapy with DFX resulted in significantly lower IMA levels in thalassemic children compared to those without chelation ($P = 0.01$). *Ghoti et al.,* (17) declared that DFX chelation's antioxidant potential was further validated when it was found to reduce oxidative stress and toxic iron species both inside and outside of cells.

The present study revealed that ischemia modified albumin at a cutoff point more than 67.14 ng/ml had sensitivity of 85% and specificity of 93% with a high significance for prediction of beta-thalassemia.

In *Moftah et al.,* (11)**,** the ROC curve revealed that IMA at cutoff > 36.1 ng/ml had sensitivity of 100% and specificity of 100% with a high significance for prediction of beta-thalassemia. Also, *Kumar et al.,* (12) declared that IMA cut off value higher than 107 ng/ml had a sensitivity of 68.9% and a specificity of 48.3%.5 In *Mousa et al.,* (13) IMA was found to have a sensitivity of 68.9% and a specificity of 48.3%, with a cutoff value higher than 107 ng/ml. They stated that in the evaluation of thalassemia, IMA may prove to be a valuable marker for the early identification of consequences.

Adly et al., (15), found that when the IMA cutoff value was 17.5 U/ml, differentiating heart disease in β-thalassemia patients had an 88.9% specificity, a 96.7% positive predictive value, and a 73.3% negative predictive value. The sensitivity was 80.5%.

In the present study, using multivariate logistic regression, both ferritin and splenectomy were statistically significant factors for prediction of significant ischemia modified albumin elevation.

Our result was in agreement with *Awadallah et al.,* (14)**.** To find out how strongly IMA was associated with the independent variables ferritin, MDA, ferroxidase, ALT, and AST, multiple linear regression analysis was run. Then, to find out what factors could be used to predict IMA levels, the results showed that ferritin was the only factor that could be used ($r=0.654$, $p=0.000$) when IMA was used as the dependent variable. In *Kumar et al.,* (12), the levels of ferritin and IMA were related using a regression analysis.

Conclusion

Children with β-thalassemia major had significantly higher levels of ischemia modified albumin compared to controls.

It may be a valuable biomarker for the early diagnosis of problems in patients with thalassemic conditions during follow-up evaluations. The rationale to support iron chelation therapy for the elimination of free iron species is backing up the claim that children on DFP had significantly lower IMA levels than those on DFX. Additionally, our data indicates that IMA was significantly greater in patients who had splenectomy as compared to those who had not. Additionally, we discovered that ferritin and splenectomy were both significant predictors of significant ischemia-modified albumin values.

Limitations

This was a single center study with a relatively small sample size, which may affect the generalizability of the findings.

We could not find the standardized value of IMA, which could specifically demarcate clinically significant oxidative stress.

This study was short-term. Time is needed to monitor and detect relations between the level of ischemia modified albumin and complication in beta thalassemic patients.

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