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MRI Evaluation of Hepatic Iron Overload in Chronically Transfused β-Thalassemic Children

Nagwan Ramadan Mahmoud [1*]; Mahmoud Ahmed Elhawy [2]; Hazem Omar [1]; Sameh Abokoura [1]

[1] Department of Interventional and Diagnostic Radiology, National Liver Institute, Menoufia University, Shebin Elkom, Menoufia, Egypt.
[2] Department of Pediatrics, Faculty of Medicine, Menoufia University, Shebin Elkom, Menoufia, Egypt.

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*Corresponding author

Email: nagwanramadan750@gmail.com

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Abstract

Background: Iron overload results from the frequent blood transfusions required for patients with chronic hemolytic anemia, such as thalassemia. MRI has become a popular noninvasive method for evaluating iron overload in different tissues.

The aim of study: was to evaluate the utility of magnetic resonance imaging [MRI] in assessing hepatic iron overload in children who were receiving several transfusions and to establish a correlation between the findings and serum ferritin levels.

Patients and Methods: 30 cases of Mult transfused children with thalassemia were included in this cross-sectional investigation. Serum ferritin, a standard biomarker of iron overload, was compared to liver iron concentration [LIC], which was determined by MRI T2*.

Results: Serum ferritin and LIC showed a strong positive correlation [r=0.575 and p<0.001]. Furthermore, there was a strong negative correlation between LIC and T2* [r=-0.565 and p<0.001]. However, there was no statistically significant association found between LIC and age, sex, splenectomy, or frequency of blood transfusions.

Conclusions: Tissue iron concentration can be measured accurately, consistently, and non-invasively by MRI T2*. The management of tissue iron overload should be improved by the widespread use of this approach, enabling earlier chelation intensification.

Keywords: Thalassemia; MRI T2*; Liver Iron Concentration; Serum Ferritin.

INTRODUCTION

The inherited hemolytic anaemia known as thalassemia major is represented by inefficient hemolysis and erythropoiesis. Since it is anticipated that 1000 children with thalassemia are born each year out of 1.5 million live births, thalassemia is a serious health issue in Egypt[1].

Blood transfusions are the preferred course of treatment for thalassemia patients. Even though it can save lives, frequent transfusions cause the tissues to get deposited with iron. Haemolysis of native and transfused red blood cells, apoptosis of defective erythroid precursors produced by inefficient erythropoiesis, and intestinal iron absorption increased by tissue hypoxia all contribute to this iron overload. The accumulation of iron that results from repeated transfusions without the use of suitable chelation therapy can have negative consequences on the liver and endocrine system and ultimately cause patient mortality, which typically happens in the second decade of life [2]. Because the liver serves as the main site of iron storage in those with hemochromatosis or transfusion-dependent anaemia, total body iron reserves are correctly reflected by liver iron concentration [LIC] [3].

One type of metalloprotein that is present in cells is ferritin. It regulates the release and storage of iron. A tiny amount typically represents the overall amount of iron in the body and is present in the circulation of healthy people. It is an acute phase reactant, and in cases of infections, inflammatory conditions, liver failure, and cancer, serum levels may be significantly higher than the amount of iron loading [4].

Due to the possibility of regional heterogeneity, liver core biopsy has significant sampling variability, which reduces its usefulness for quantitative evaluation of parenchymal liver disease [5]. Furthermore, CT can identify severe iron overload; however, neither US nor CT can accurately quantify hepatic iron overload. For these causes, the best methods for measuring liver iron are non-invasive imaging techniques that show the entire liver [6].

Nowadays, MRI is a vital tool in the treatment of thalassemia patients. It offers a number of advantages over other metrics, such as serum ferritin and liver biopsy, because it may evaluate iron overload in many organs noninvasively and without contrast. Both signal intensity ratio techniques and relaxometry methods [T2*/T2] can be used to measure LIC [7].

To change the contrast between different organs, the MRI machine can produce images at varying observation or "echo" times. With longer echo times, all organs darken, but iron-containing organs darken more quickly. This is because, although the magnetic field in a clinical scanner is very homogeneous, the presence of iron in tissues causes localised magnetic field disturbances, which accelerate the darkening of the images. T2* represents the echo time necessary for a tissue to become twice as dark. R2*, the image's rate of darkening, is an alternative way to express image darkening. Since R2* is directly correlated with iron concentration, some researchers would rather report R2* values than T2* values. It is easy to change one representation to another because R2* values are just 1000/T2* and vice versa [8].

Using the characteristic time constants of signal degradation for gradient-echo and spin-echo magnetic resonance imaging, respectively, T2 and T2* were measured in milliseconds. Transverse relaxometry techniques, which detect the signal at several echo times [TEs] to determine the decay time, can be used to quantify these time constants. The rate of signal decay, or R2 [1/T2] or R2* [1/T2*], both with units of second−1, is preferable in the context of LIC quantification since R2 and R2* rise monotonically with increasing LIC **[Figures 1, 2]**.

Henninger *et al*. [9] reported that both milligrams per gramme and micromolar per gramme are used to display LIC units. The color scale represents normal, mild overload, moderate overload, moderate-to-severe overload, and severe overload, arranged from left to right **[Figure 3, Table 1]**.

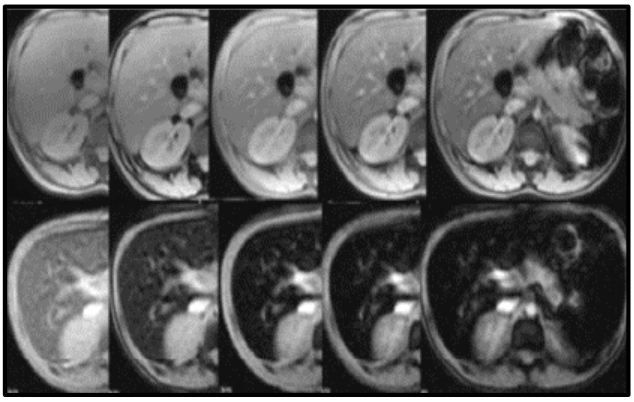

Figure 1: Hepatic GRE sequence on MRI Up: The liver exhibits slow signal loss in the images from the five initial echoes. The R.2" is 47Hz, suggesting the lack of iron overload and a LIC of 1.39 mg Fe/g dry liver. Down: The liver's signal is rapidly deteriorating. The R.2 is 700 Hz, indicating a significant iron overload of 18 mg Fe/g dry liver [8]

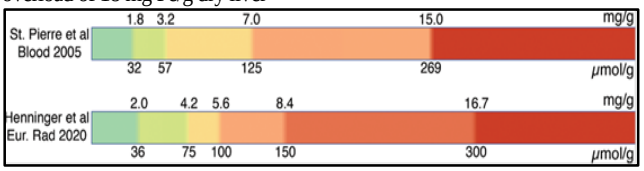

Figure [2]: St Pierre's summary of the graphical representation of commonly used liver iron concentration [LIC] thresholds [10].

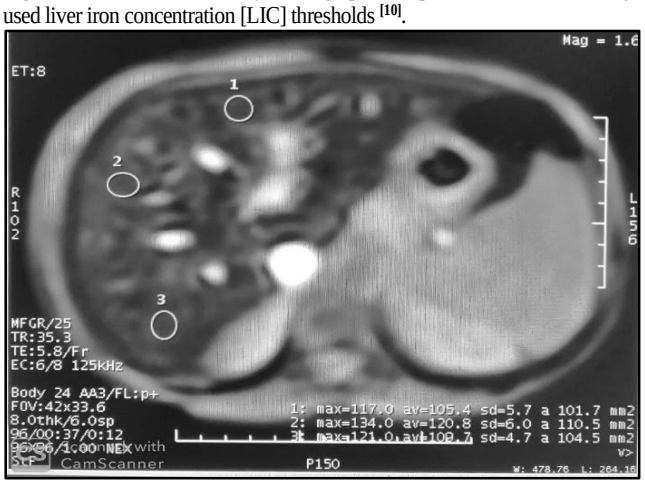

Figure [3]: Hepatic T2* of child with beta thalassemia. An 8 years old male child diagnosed with thalassemia major disease. Clinically, the patient exhibited hepatomegaly, no splenomegaly and anemia on regular blood transfusion every 30 days. Laboratory investigation revealed elevation in serum ferritin level 357 ng/ml [normal range: 21.8-247.6 ng/ml] along with normal bilirubin 0.8 mg/dl [normal range: 0.1-1.2 mg/dl] and normal albumin 4.2 mg /dl [normal range: 3.4-5.4 mg/dl]. Notable, normal AST 24 IU/L [normal range: 10-34 IU/L] and normal ALT 36 IU/L [normal range: 10-44 IU/L]. MRI [T2*] performed on liver resulting in elevated T2* [111 MS] which means LIC 6.02 ng/g denoting mild hepatic iron overload.

Table [1]: relation between liver iron concentration, T2* and hepatic iron overload [9]

Iron loading	LIC	T2*
No iron load	<2 mg/g	>11.4 Ms
Mild iron load	2 – 7 mg/g	3.8-11.4 Ms
Moderate iron load	7 – 15 mg/gm	1.8-3.8 Ms
Sever iron load	>15 mg/g	<1.8 Ms

THE AIM OF THE WORK

The purpose of this study was to evaluate the utility of magnetic resonance imaging [MRI] in assessing hepatic iron overload in children who were receiving several transfusions and to establish a correlation between the findings and serum ferritin levels.

METHODOLOGY

Thirty children, 50.0% male and 50.0% female, with thalassemia, with a mean age of 11.57 ± 3.81 years [ranging from 6-18 years], participated in this cross-sectional study. The Menoufia University Hospital's Research Review Committee accepted the study protocol, and each subject provided informed permission prior to the procedure. Every child was getting testing using a 1.5 Tesla MRI scanner. MRIT*2 was used to evaluate the iron content of the liver, and serum ferritin levels were compared. From June 2023 to June 2024, our study was conducted at Menoufia University's National Liver Institute Hospital's diagnostic medical imaging and intervention radiology department.

Inclusion criteria: children clinically diagnosed thalassemia, since their early years, all of the children have had iron chelation therapy in addition to a regular transfusion program.

Exclusion criteria: patients with liver decompensation, co-existence of chronic viral hepatitis, autoimmune hepatitis and other metabolic diseases of the liver, patients who are contraindicated to perform MRI [Claustrophobia], patients who refused the examination, images of non-diagnostic quality due to severe motion artefacts.

MRI examination: Every patient was examined using an Optima MR450W GEM 1.5 T Elite MRI scanner [GE Healthcare, Milwaukee, WI, USA]. For liver imaging, a phased-array thoracic coil was utilized.

MRI technique: Every metallic thing was taken away from the patient's body. Using a body coil, we placed the supine patient head first into the MRI machine. Patients were told how crucial it was to remain calm and not move during the assessment.

Hepatic iron overload MRI procedure comprising: Gradient echo [GRE] with multiple axial images with different TE, TR was 100ms, Flip angle=20 and slice thickness was 10mm with no gap interval. Region of Interest [ROI] was created using software designed specifically for post-image processing. Analyses of signal intensity were carried out on the liver's periphery, away from the main vessels. Two radiologists, a consultant having a minimum of fifteen years of expertise in body imaging and an experienced radiology specialist with over 8 years of experience in abdomen MRI imaging, performed the image interpretation. The radiologists were not given access to the final diagnostic and clinical data.

Statistical analysis: SPSS v26 [IBM Inc., Chicago, IL, USA] was used for statistical analysis. The unpaired Student's t-test was used to compare the quantitative variables between the two groups. The variables were provided as mean and standard deviation [SD]. To examine the frequency and percentage [%] of the qualitative variables, the Chi-square test was employed. A two-tailed P value less than 0.05 was considered statistically significant. The Pearson correlation coefficient was used to perform correlations.

RESULTS

Thirty patients were included in the study; their ages ranged from six to eighteen, with a mean [± SD] of 11.57 ± 3.81 years. Fifteen [50.0%] males and fifteen [50.0%] females were present. A total of 7 patients, comprising 23.0% of cases, had splenectomy. The patients had frequent blood transfusions as follows, with the frequency of transfusions ranging from 15 to 31 days: There are four [14.0%], seven [23.0%], eighteen [60.0%], and one [3.0%] every thirty, sixty, and forty days **[Table 2, Figure 4]**. The participants in the study had serum ferritin levels ranging from 357 to 8914 ng/ml, with a median value of 3909.5. The T2* value varied between 0.8 and 8.06, with a median value of 2.99 ms. With a median value of 12.8, the LIC ranged from 5.4 to 23.8 mg/g **[Table 3; Figures 5, 6 and 7]**.

Among the studied patients, its features were as follows: Ten [33.3%] experienced mild overload, ten [33.3%] experienced moderate overload, and ten [33.3%] experienced severe overload. There was no statistically relationship between LIC and splenectomy and sex **[Table 4]**. There was a strong negative association between T2* and LIC, while serum ferritin [i.e., serum ferritin [r: 575; p<0.001]] showed a high positive correlation with LIC. Although there is no discernible relationship between LIC and age or the frequency of blood transfusions **[Table 5; Figures 8 and 9]**.

Hepatosplenomegaly and anemia were observed in the patient's clinical records, with blood transfusions occurring every 21–23 days. A laboratory analysis indicated raised direct bilirubin 1.9 [normal range: 0.1-1.2] and normal albumin 4.2 [normal range: 3.4-5.4]. notably, elevated AST 52 [normal range: 10-34] and elevated ALT 52 [normal range: 10-44]. A liver MRI [T2*] revealed low T2* 0.91 MS, which indicates LIC of 20.03 mg/g, indicating severe hepatic iron overload **[Figure 10, 11]**.

Table [2]: Demographic data and other different parameter of the studied patients

		Statistics [n=30]
Age [years/	Mean ± SD Range	11.57 ± 3.81 6 - 18
Sex	Male [%] Female [%]	15 [50.0%] 15 [50.0%]
Splenectomy	Yes [%] No [%]	7 [23.0%] 23 [77.0%]
Frequency of blood transfusion [in days]	Mean ± SD Range	23.9 ± 4.96 15 - 31

Table 3: Distribution of the studied cases based on serum ferritin and MRI parameters

		Statistics [n=30]
Serum ferritin [ng/ml/	Median [IQR] Min. – Max.	3909.5 [1307.5-5812.3/ 357 – 8914
T2* [Ms/	Median [IQR/ Range	2.99 [1.33-5.1/ 0.8-8.06
LIC [mg/g/	Median [IQR/ Range	12.8 [3.1-18.2/ 5.4–23.8

Table [4]: relation between LIC and other various characteristics

		LIC		P value
		Median [IQR]	Range	
Sex	Female	2.96 [1.1-4.4]	0.8-7.7	0.81
	Male	3.23 [1.3-6.2]	0.93-8.1	
Splenectomy	No	2.96 [1.1-5.9]	0.8-8.1	0.34
	Yes	3.2 [2.5-3.8]	2.1-4.4	

Significant as P value ≤ 0.05; LIC, liver iron concentration.

Table [5]: LIC correlation with several parameters

	LIC	
	r	*P*
T2	-.565	<0.001*
Serum ferritin	.575	<0.001*
Age	-.235	0.105
Frequency of blood transfusion	.247	0.187

*Significant as P value ≤ 0.05. r: Pearson Correlation. *: Statistically significant at P ≤ 0.05; LIC, liver iron concentration.

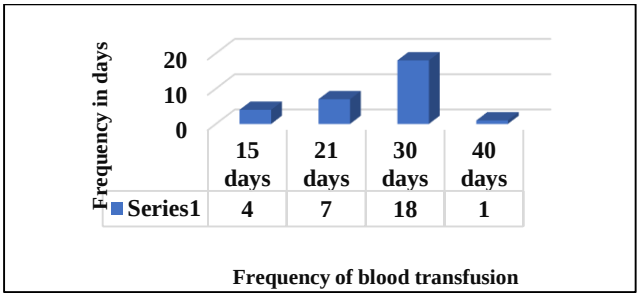

Figure [4]: Blood transfusion frequency among study cases.

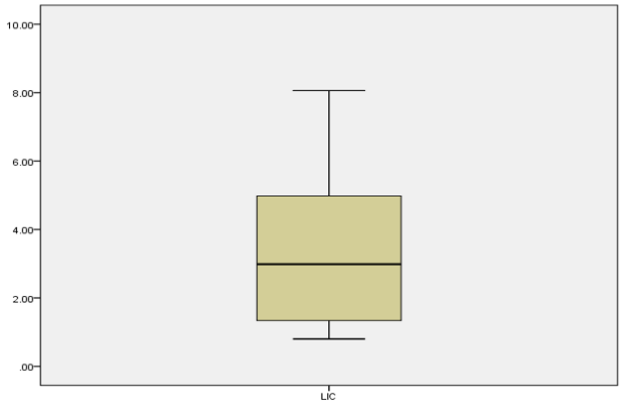

Figure [5]: LIC in the studied patients

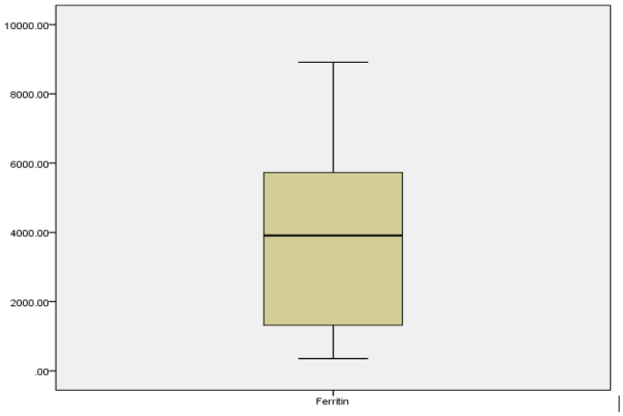

Figure [6]: Serum ferritin in the studied patients

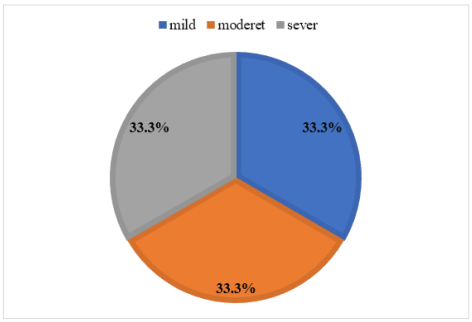

Figure [7]: characteristics of LIC among the studied cases

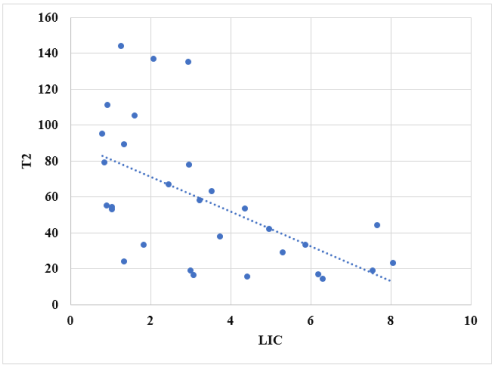

Figure [8]:Correlation between the T2 and LIC

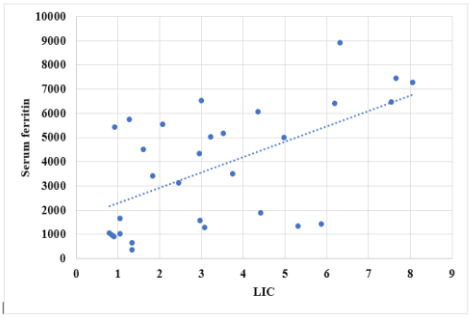

Figure [9]: Correlation between the serum ferritin and LIC.

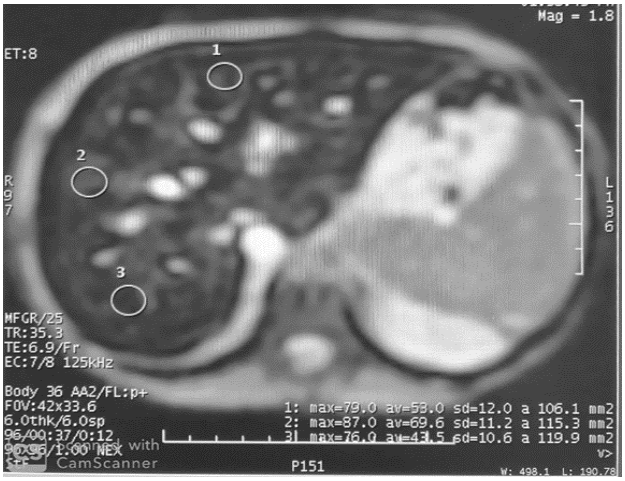

Figure [10]: A 10 years old female child diagnosed with thalassemia major disease. Clinically, the patient showed anemia and hepatosplenomegaly when receiving regular transfusions of blood every 23–25 days. A laboratory analysis found that the blood ferritin level was up to 1270 ng/ml [normal range: 21.8-247.6], and the albumin level was normal at 3.6 [normal range: 3.4-5.4] and the bilirubin level was elevated to 1.7 [normal range: 0.1-1.2]. Specifically, higher ALT 51 [normal range: 10-44] and AST 44 [normal range: 10-34]. A liver MRI [T2*] revealed a low T2* of 3.09 ms, indicating a moderate hepatic iron excess [LIC 9.5mg/g].

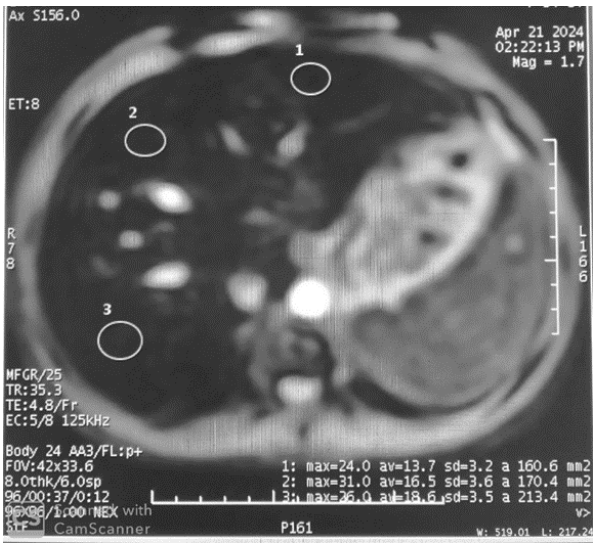

Figure [11]: 11 years old female child diagnosed with thalassemia major disease. Clinically, the patient exhibited hepatosplenomegaly and anemia on regular blood transfusion every 21-23 days. Laboratory investigation revealed elevation in serum ferritin level 7255 ng/ml [normal range: 21.8-247.6 ng/ml] along with elevated bilirubin 1.9 mg/dl [normal range: 0.1-1.2 mg/dl] and normal albumin 4.2 mg/dl [normal range: 3.4-5.4 mg/dl]. notably, elevated AST 52 IU/L [normal range: 10-34 IU/L] and elevated ALT 52 IU/L [normal range : 10-44 IU/L]. MRI [T2*] performed on liver resulting in low T2* [16.3 ms] which means LIC 0.91 ng/g denoting sever hepatic iron overload.

DISCUSSION

Since iron overload is a major side effect of repeated blood transfusions used as a long-term treatment for thalassemia, which is a serious disease, quantifying the amount of iron deposited in different organs in patients receiving multiple transfusions is crucial for the efficient monitoring of iron chelation therapy. The only methods used to measure the liver iron concentration in the past were biopsy and ferritin levels [11]. However, having a serum ferritin [SF] level alone is insufficient. It is often used as a marker of both acute and chronic inflammation and an acute phase reactant. It is nonspecifically elevated in a variety of inflammatory conditions, such as acute infection, malignancy, rheumatoid arthritis and other autoimmune disorders, chronic liver and kidney diseases, and some other inflammatory conditions [12].

The conventional gold standard for diagnosing iron overload is tissue biopsy; however, iron deposition is often patchy. So, biopsies are an invasive, risky procedure that has the potential to miss the sites of deposition and yield a false negative result. Additionally, the efficacy of this evaluation is diminished by the risk and discomfort that patients experience during a liver biopsy, as well as the weak correlation between liver fibrosis and iron content particularly if it needs to be repeated often [11].

Therefore, a crucial first step in monitoring chelation therapy and diagnosing organ siderosis in thalassemia patients is the use of specific, non-invasive, quick, single MRI sequences like T2* for the identification and quantification of hepatic iron overload [13].

The purpose of this study was to highlight the utility of magnetic resonance imaging [MRI] in assessing the iron accumulation in the liver of patients receiving regular transfusions who have thalassemia.

Thirty B-thalassemia Major patients [15 females and 15 males] with a mean age of 11.57 ± 3.81 years [ranged: 6-18 years] participated in our study. Every patient received iron chelation treatment in addition to routine transfusions.

No significant correlations between LIC and age, sex, or the frequency of blood transfusions were found in our investigation. This outcome is consistent with numerous earlier research projects carried out by **Atmakusuma *et al*.** [14]. Similarly, **Karimi *et al*.** [15] stated that there was no obvious relationship between of the characteristics of thalassemic individuals and LIC.

Additionally, our study did not find any significant association between LIC and splenectomy, which is consistent with research conducted by **Mohammad zadeh *et al*.** [16] and by **França and Carvalho** [2] and **El-Shanshory *et al*.** [17] who indicated that the timing of the splenectomy and its impact on LIC and total body iron were shown to be insignificant.

Our research revealed a negative relationship between T2* and LIC. The findings of this research were in keeping with those of other research by **Öncel *et al*.** [11] and **El-Shanshory *et al*.** [17] who discovered that LIC is strongly correlated with T2* and that the more iron overload in the liver, the more the signal intensity [SI] on MR images decreases, with T2* representing the progressive darkening of the liver parenchyma with increased TE.

These findings can be clarified by iron's paramagnetic characteristics, which can alter tissue susceptibility and alter the magnetic field, causing a drop in [T2*, T2] in response to significant iron overload. This result could also be assigned to the mechanism of magnetic resonance imaging [MRI], water protons are imaged when they diffuse around iron deposits in target tissue, such as the liver and heart, rather than the iron itself. The homogeneity of the magnetic field in tissues rich in iron is disrupted by the iron's micro magnetic properties. The protons in the moving water undergo markedly distinct magnetic profiles and desynchronies from one another. As a result, the image darkens proportionately to the amount of iron present [18].

Our findings were supported by **Marini *et al*.** [19] demonstration that there is a statistically significant positive correlation and a statistically significant negative association between serum ferritin and liver LIC and liver T2*, respectively.

Limitations and recommendations of the study:

The absence of a control group of children with thalassemia who aren't infected with HCV is a major research drawback. We neglected to take into account the various chelation therapy regimens, assess chelation therapy responses, and track alterations in T2* values. The limited sample size.

We were unable to retrieve those details for every patient from the system due to the retrospective nature of the investigation. Numerous illnesses that impact serum ferritin levels apart from variations in the body's iron loads, including vitamin C insufficiency, fever, liver injury both acute and chronic, hemolysis, and inefficient erythropoiesis, can complicate the interpretation of serum ferritin values. These conditions occur frequently in b-thalassemia major's patients. Hepatic fatty infiltration may potentially have an impact on T2* and, hence, liver iron concentration levels.

Numerous randomized controlled clinical trials with larger sample sizes are advised. During chelation therapy, the liver must be

routinely examined for iron deposition because the liver's involvement is one of the main factors determining death in thalassemia. MRI-based organ evaluation is now the gold standard and ought to be applied for determining the iron concentrations in different organs, especially the liver.

Conclusion:

Tissue iron concentration can be measured accurately, consistently, and non-invasively by MRI T2*. The management of tissue iron overload should be improved by the widespread use of this approach, enabling earlier chelation intensification.

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