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The role of cardiac T2* magnetic resonance imaging in the assessment of myocardial iron concentration in patients with beta-thalassemia major

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ABSTRACT

Background: Beta-thalassemia is a group of inherited blood disorders that are characterized by reduced levels of functional hemoglobin. These patients require lifelong blood transfusions, leading to iron deposition in various tissues. Prompt detection of myocardial iron helps to assess the extent of myocardial damage and its complications. **Aims and objectives:** Our study aims to establish the role of T2* cardiac magnetic resonance imaging (MRI) and its comparison with serum ferritin levels in detecting iron overload in beta-thalassemia major (TM) patients. **Materials and Methods:** This prospective study included 30 pediatric patients admitted to our institute with beta-TM. The patients underwent T2* cardiac MRI examinations, myocardial iron quantification was assessed, and patients were divided into groups based on the severity of iron overload. **Results:** In this study, there were 18 males and 12 females. Out of the total studied cases, 15 (50%) showed no evidence of iron overload, 8 (26.67%) showed mild, 4 (13.33%) showed moderate, and 3 (10%) showed severe cardiac siderosis, based on the cardiac T2* values obtained. **Conclusion:** T2* cardiac MRI is an accurate and invaluable tool that helps to detect iron overload in beta-TM.

Key words: Beta-thalassemia; Ferritin; Iron overload; Myocardial iron concentration; T2* cardiac magnetic resonance imaging

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INTRODUCTION

Beta-thalassemia is a group of inherited hematological disorders, typically inherited in an autosomal recessive manner in which there is reduced or absent synthesis of the beta-chain of hemoglobin, which leads to microcytic anemia. It is caused by mutations in the hemoglobin beta-gene (HBB) gene.[1]

Beta-thalassemia is a spectrum of disorders that includes thalassemia minor, thalassemia intermedia, and thalassemia major (TM), of increasing severity of anemia.[2] In people with TM or thalassemia intermedia, both copies of the HBB gene are mutated. Common symptoms encountered in beta-thalassemia patients include paleness, weakness, and fatigue.

Patients with beta-TM require a lifelong blood transfusion to prevent anemia. Repeated blood transfusion causes iron deposition in various organs such as the heart, liver, and endocrine glands, leading to iron overload.[3] Intracellular free iron in the myocardium can induce tissue damage, cardiac rhythm abnormalities, and heart failure, which is the leading cause of death among TM patients.[4]

There are many different methods to measure iron levels in other organs. These include serum ferritin,

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echocardiography, liver biopsy, and T2* liver and cardiac magnetic resonance imaging (MRI).

Cardiac T2* MRI is now considered the gold standard for iron concentration because of its high sensitivity. Cardiac MRI is more reliable than serum ferritin, biopsy, and echocardiography. It is the non-invasive, non-ionizing, and most precise method to measure iron overload. It is also used to monitor chelation therapy.[5]

Moving iron particles with their strong ferromagnetic effects cause inhomogeneity of the magnetic field. Hence, moving water protons have varying velocity and show loss of synchronization with one another.[6]

This yields a black image directly proportional to iron concentration.[7,8] The presence of iron deposits causes the shortening of T2* values.[9] A rise in the T2* value implies good heart function.[10]

Based on the cardiac T2* value obtained, four categories of iron overload[11,12] are made (Table 1).

The objective of this study was to analyze the relationship between myocardial iron concentration (MIC), myocardial T2* values, and serum ferritin levels.

Aims and objectives

Our study aims to establish the role of T2* cardiac magnetic resonance imaging (MRI) and its comparison with serum ferritin levels in detecting iron overload in beta-thalassemia major (TM) patients.

MATERIALS AND METHODS

This prospective observational study included 30 pediatric patients with beta-thalassemia whose ages ranged from 7 to 15 years. These patients were not on any chelation therapy. Written informed consent was obtained from the patient's relatives. Cases with potential contraindications to MRI scans, such as claustrophobia, cochlear implants, metallic items, and pacemakers, were removed from the study. Then, after a complete history taking, clinical examination, and laboratory testing, patients were exposed to an MRI examination. Serum ferritin levels of the patients obtained in the past 3 months before the MRI scan were also recorded.

An Institutional Ethical Committee clearance was obtained before the study with clearance number IESC/FP/2021/51.

The MRI examination was done using a Siemens Magnetom Vida 3T MRI machine. A cardiac gated MRI was performed supine with head first and hands in super-abduction. An 18-channel body array Siemens Healthineers coil was used. MRI parameters used are given in (Table 2).

MRI protocol:

1. Three plane localizers with two chambers, four chambers, and short-axis views
2. T2* - single breath-hold multi-echo gradient echo sequence (white blood) at eight different echo times, that is, 2.5–17.4 ms, increasing in 2.1 ms increments, of a single mid-ventricular short-axis view was taken.

To eliminate susceptibility artifacts, cardiac MRI T2* values were measured using the region of interest (ROI) in the interventricular septum. The ROI was automatically replicated into exact locations on images from various TEs.

T2* was converted to its inverse, R2*, using the following equation:

$$T2^*=1000/R2^*$$

By halving the R2* value obtained at 3 T and dividing by 1000, one may estimate the comparable T2* value obtained at 1.5 T. The importance of T2 * at 1.5 T was used to categorize the iron overload.[13]

A signal intensity-time curve was plotted with signal intensity values obtained at the ROI at different TEs for each case, similar to the study done by Carpenter et al.[14] Each patient was classified as having no overload, mild overload, moderate overload, or severe overload based on the T2* values obtained.

Statistical analysis

IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp. was used

Table 1: Categories of iron overload based on T2* values

T2*(ms)	Category	Cardiac Function
>20	None	None
15–20	Mild	None or rarely associated with cardiac dysfunction
10–15	Moderate	Risk of cardiac decompensation
<10	Severe	Significantly increased risk of cardiac decompensation

Table 2: Parameters for the MRI scan

Parameter	Value
Slice thickness	10 mm
DFOV	400 mm
Flip angle	20°
Matrix	256×96
TE	2.45–17.43 ms with 2.1 ms increments
TR	200

DFOV: Displayed field of view, TE: Time to echo, TR: Repetition time

to perform the statistical analysis. The data were entered into an Excel spreadsheet. One-way analysis of variance (ANOVA) test was used to assess any significant difference between the four categories. *Post hoc* Tukey test was used to compare independent variables in the four categories of iron overload.

The probability of error at 0.05 was considered significant, while at 0.01 and 0.001, it is highly significant.

RESULTS

The study was performed on 30 individuals with beta-TM, 18 (60%) were males, and 12 (40%) were females. The mean age of patients was 11.2+1.93 years, and its range was 7–15 years. The mean serum ferritin level was 3827.43+1599.94 ng/dl.

Out of the total 30 patients, 15 (50%) showed no evidence of iron overload, 8 (26.67%) showed mild, 4 (13.33%) showed moderate, and 3 (10%) showed severe cardiac siderosis, based on the cardiac T2* values obtained (Figures 1 and 2). The mean of cardiac T2* was 31.937+27.32 ms (8.7–98.9). The mean MIC obtained was 1.26+0.89 mg/g (0.13–3.22).

Comparison of age using one-way ANOVA test shows that the mean value of the no overload category (11.67) is the highest, followed by severe (11.33), mild (11.13), and least in moderate (9.5). This difference is statistically not significant, with a test value of 1.378 and P=0.272. The *post hoc* Tukey test shows that the difference between each of the following categories was statistically not significant (Table 3).

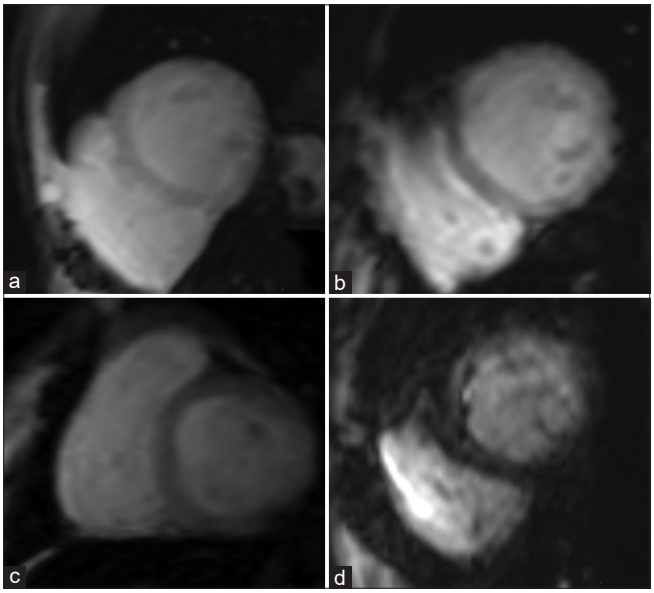

Figure 1: GRE T2* images in mid-ventricular short-axis view at TE of 4.59, demonstrating: (a) No iron overload, (b) mild iron overload, (c) moderate iron overload, and (d) severe iron overload (representing progressive blackening of the myocardium from a to d)

Comparison of T2* using one-way ANOVA test shows that the mean value of no overload (49.946667) is the highest, followed by mild (16.875), moderate (11.7025), and least severe (9.033333). This difference is statistically significant, with a test value of 10.919 and P<0.001. The *post hoc* Tukey test shows that the difference between the no overload category and each of the other three categories was statistically significant. In addition, the difference between the mild and moderate categories was statistically significant. On the other hand, the difference between mild and severe categories and between moderate and severe categories was statistically not significant.

Using the one-way ANOVA test for comparison of MIC, the mean value of severe (3.05) is the highest, followed by moderate (2.235), mild (1.44625), and least in no overload (0.548). This difference is statistically significant, with a test value of 109.023 and P<0.001. In addition, the *post hoc* Tukey test shows that the difference between each of the following categories was statistically significant.

Comparison of serum ferritin (ng/ml) using one-way ANOVA test shows that the mean value of the severe category (5936.67) is the highest, followed by moderate (4625.75), no overload (3719.67), and least in mild (2839.38). This difference is statistically significant, with a test value of 6.583 and P=0.004.

The *post hoc* Tukey test shows that the difference between mild and severe categories was statistically significant, whereas the difference between the rest of the categories was statistically not significant. Using Pearson's correlation, T2* and MIC (mg/g) showed an excellent negative correlation (Figure 3) which was statistically significant with P<0.001, whereas MIC (mg/g) and serum ferritin (ng/ml) showed a moderate positive correlation which was not significant with P=0.127.

DISCUSSION

In individuals with TM, iron overload-induced heart failure is one of the most prevalent causes of morbidity and mortality.[15] Although bone marrow transplantation can help certain beta-TM patients, blood transfusions and iron chelation are still the most common treatments.[16] The unpredictability of cardiac iron accumulation and the late onset of symptoms contribute to a delay in diagnosing iron-induced cardiomyopathy.[11] Cardiomyopathy caused by iron overload can be reversed if chelation treatment is initiated early.[17]

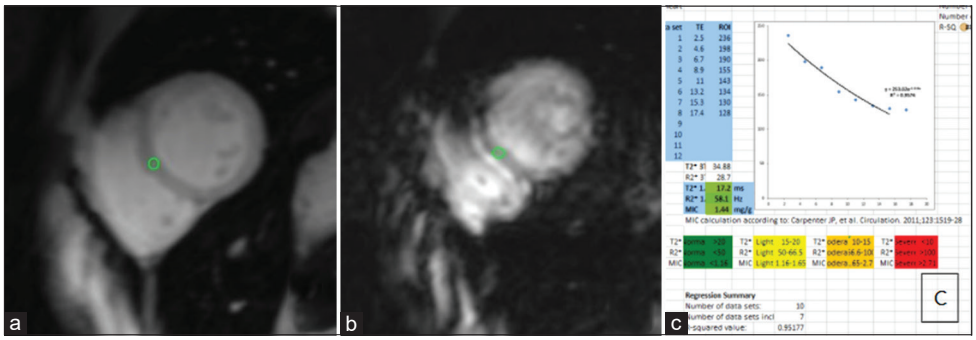

Figure 2: GRE T2* sequence of mid-ventricular short-axis view in a subject with mild iron overload (green circle in the interventricular septum represents the region of interest) (a) TE of 2.45 with a mean SI of 236; (b) TE of 17.43 with a mean SI of 128; and (c) corresponding signal intensity time curve

Table 3: *Post hoc* Tukey test demonstrating the pair-wise comparison of the various parameters in the four categories

Dependent Variable	Comparison Group	Compared with	Mean difference	Standard error	P-value
Age	No Overload	Mild	0.542	0.832	0.914
		Moderate	2.167	1.069	0.204
		Severe	0.333	1.202	0.992
	Mild	Moderate	1.625	1.164	0.513
		Severe	–0.208	1.286	0.998
	Moderate	Severe	–1.833	1.451	0.594
T2*	No Overload	Mild	33.071	9.311	0.008*
		Moderate	38.244	11.969	0.018*
		Severe	40.913	13.452	0.026*
	Mild	Moderate	5.172	13.025	0.978
		Severe	7.841	14.399	0.947
	Moderate	Severe	2.669	16.245	0.998
MIC mg/gm)	No Overload	Mild	–0.8982	0.112	<0.001*
		Moderate	–1.6870000	0.143	<0.001*
		Severe	–2.502	0.161	<0.001*
	Mild	Moderate	–0.7887500	0.156	<0.001*
		Severe	–1.603	0.172	<0.001*
	Moderate	Severe	–0.8150000	0.194	0.002*
Serum ferritin (ng/ml)	No Overload	Mild	880.292	609.268	0.484
		Moderate	–906.083	783.135	0.658
		Severe	–2217	880.167	0.08
	Mild	Moderate	–1786.375	852.218	0.181
		Severe	–3097.292	942.163	0.014*
	Moderate	Severe	–1310.917	1062.903	0.612

*Indicates statistical significance, MIC: Myocardial iron concentration

A serum ferritin level above 1800 mg/L is related to an increased MIC, whereas levels above 2500 mg/L are associated with cardiac dysfunction.[16,18] According to the several recent studies, the serum ferritin level is not indicative of myocardial iron loading as it can be affected by liver disease, Vitamin C levels, inflammation, and infection, making its assessment unreliable.[7,19]

Echocardiography is another method, but not reliable for detecting iron overload in early stages.[20]

Liver biopsy, although regarded as the best approach for determining iron overload, is invasive and provides an inappropriate representation of iron as the distribution of iron in the liver is heterogeneous.[21]

Cardiovascular magnetic resonance (CMR) T2* is a non-invasive technique for identifying iron overload in the heart that is widely utilized. The CMR T2* is a reproducible method for determining myocardial iron. It was found to be associated with both systolic and diastolic heart function.[22] Furthermore, CMR T2* can be utilized to detect the myocardial iron level before symptoms of iron overload cardiomyopathy appear. The only drawback of CMR T2* is that it is a relatively expensive method compared to other methods for detecting iron overload.

In the present study, T2* was used to evaluate myocardial iron levels. The youngest individual who developed iron overload as measured by cardiac T2* was a 7-year-old male. There was no significant association between age

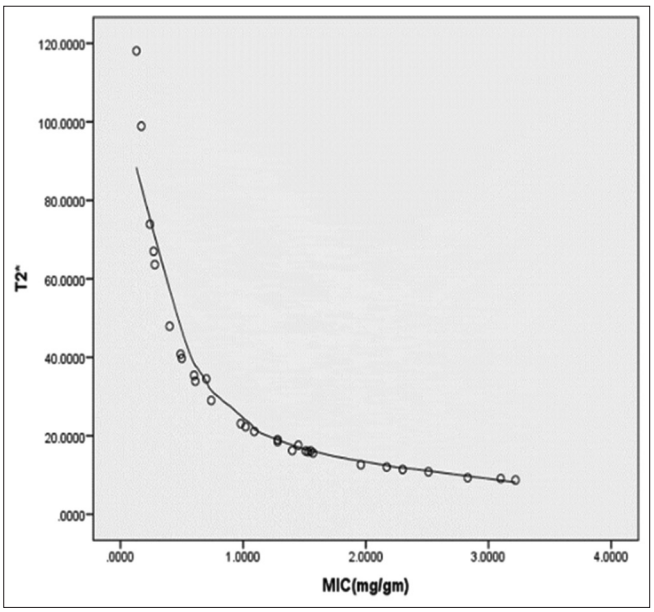

Figure 3: Graph depicting exponential curve with an excellent negative correlation between T2* and myocardial iron concentration which is statistically significant

and the cardiac T2* value (P=0.272). Similar results were obtained in a study by Shehata et al., where cardiac T2* values showed no correlation with age (p=0.6).[3]

However, Shamsian et al., discovered a direct correlation between age and cardiac T2*MRI (r=0.18, P=0.08).[23] In our study, the mean T2* result did not significantly differ between male and female groups (P=0.970). Similar results were obtained in the study by Shamsian et al., (P=0.47).[23]

In our study, the serum ferritin levels varied from 2000 to 7873 mg/dl in this research. No significant association between serum ferritin and cardiac T2* was noted. Puliyel et al.,[24] stated in similar research that serum ferritin cannot be used to assess whole-body iron levels and that there is minimal correlation between cardiac T2* and serum ferritin. However, in a study done by Kahnooji et al.,[25] serum ferritin showed a positive correlation with the level of myocardial iron load (r=0.257, P<0.001).

Hence, T2* cardiac MRI has become the preferred technique to diagnose, measure, and surveil myocardial iron and guide chelation therapy to prevent complications and reduce mortality.

Limitations of the study

This research was a small study and involved patients who had not yet received any iron chelation therapy nor had any cardiovascular events in the past. Long-term follow-up for these patients with serial T2* cardiac MRI was not done in our study, which would otherwise help assess the prognosis of iron overload and its complications.

CONCLUSION

Our study suggested an association between cardiac T2* levels and myocardial iron content. In addition, no significant association between serum ferritin and MIC values was observed. Thus, T2* MRI offers a precise assessment of the iron overload in individuals with thalassemia and helps in the early detection of patients with a risk of iron-induced cardiomyopathy and categorizes them according to the severity.

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Authors Contribution:
TMK – Concept and design of the study and prepared first draft of manuscript; **VPS –** Prepared first draft of manuscript, interpreted the results, reviewed the literature, and manuscript preparation; **SUZ –** Concept, coordination, and statistical analysis. **SMJS –** Statistical analysis and revision of manuscript; and **RK –** Statistical analysis and revision of manuscript

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