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Role of magnetic resonance imaging (MRI) in liver iron quantification in thalassemic (thalassemia major) patients

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Abstract

Background Iron overload is a major problem in beta thalassemia patients due to repeated blood transfusions. The liver is the first organ to be loaded with iron. An accurate assessment of iron overload is necessary for managing iron chelation therapy in such patients. Iron quantification by MRI scores over liver biopsy due to its non-invasive nature.

Methods Fifty-one patients with thalassemia major were subjected to 3.0-T MRI. Multiecho T2* sequence was used to cover the entire liver. Region of interest (ROI) was placed in three areas with maximum signal change, and an average T2* value was obtained. Similarly, a single ROI was placed at the mid-interventricular septum in the heart, and T2* value was obtained. T2* values so obtained were converted to iron concentration with the help of a T2* iron concentration calculator. The liver iron values were correlated with serum ferritin value.

Results There was a significant negative correlation between liver iron concentration (LIC) and T2* value of the liver ($r = -0.895$, $p < 0.01$) and between cardiac iron concentration (CIC) and T2* value of the heart ($r = -0.959$, $p < 0.01$). There was a slight positive correlation between LIC and serum ferritin ($r = 0.642$, $p < 0.01$) and no correlation between CIC and serum ferritin ($r = -0.137$, $p = 0.354$).

Conclusions MRI is a useful tool to titrate the doses of chelating agents as it is accurate and non-invasive, does not involve radiation hazards and hence can be repeated as and when needed. Simultaneous assessment of cardiac iron overload is an added advantage of MRI.

Keywords Thalassemia, Liver iron concentration, Cardiac iron concentration, T2* imaging

Aim: The present study aimed to evaluate the usefulness of T2*W MRI in assessing iron overload in thalassemia major patients and if it can help in titrating chelation therapy.

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Background

Thalassemia is an autosomal recessive disorder of haemoglobin synthesis. Most patients, particularly those with thalassemia major, need frequent blood transfusions, which leads to the accumulation of iron in various organs especially the liver, heart and endocrine organs. The liver is the first organ to be loaded with iron [1].

Initially, transferrin binds with excess iron, and when the capacity of transferrin to take excess iron is surpassed, free iron appears and starts accumulating in the organs. Free iron is toxic to the cells and leads to tissue damage and causes morbidity and mortality. It leads to liver fibrosis, heart failure, arrhythmia, etc. Humans have

no active mechanism to excrete excess iron. Almost all patients with thalassemia major who regularly receive blood transfusions accumulate toxic amounts of iron by the age of 10 years or earlier and acquire potentially lethal iron burden by early adolescence, if not given any treatment to remove excess iron. Iron toxicity is the most important factor in causing organ damage in thalassemia patients and makes effective chelation an absolute requirement to alleviate its impact. Accurate assessment of iron overload is therefore necessary for managing iron chelation therapy in beta thalassemia patients who receive multiple transfusions [2].

Adjustment in doses of iron chelation therapy is very crucial in patient management which in turn depends on the extent of iron overload. There are different methods to measure iron overload. Serum ferritin is a widely used marker to measure iron overload, but it is also an acute phase protein, and hence, its levels can be influenced by inflammation, use of chelation therapy, infection, vitamin C level and liver damage [3].

Clinically, it is believed that the amount of serum ferritin (SF) reflects the amount of iron stored in the liver. Although there is a broad correlation between SF level and liver iron, the prediction of iron loading from SF can be unreliable [4].

Liver biopsy is the gold standard to detect iron overload, but it is invasive and associated with various complications. Also, the distribution of iron in the liver is uneven, so it is difficult to get the best biopsy specimen.

Recently, biopsy is being replaced by magnetic resonance imaging (MRI) technique. T2* MRI can measure the concentration of iron in the liver and heart, is noninvasive and is beneficial for appropriate chelation treatment for individual persons [5].

Methods

The study was conducted in 51 patients with thalassemia major (age 5–25 years, mean age 15.23 ± 5.2 years, 37 males and 14 females) more than 5 years of age receiving repeated blood transfusions registered with thalassemia day care centre of a tertiary care centre. Patients already having any cardiac complication not associated with iron overload were excluded from the study. All patients except 2 had thalassemia facies. The frequency of blood transfusion ranged from once in 15 days to once in 20 days. Most patients were given oral chelation therapy (deferiprone and/or deferasirox). The haemoglobin level of most of the patients was maintained between 8 and 9 g/dl. The total leukocyte count of all the patients except 1 (who had a mild increase in leukocyte count—11,500/cc) was within the normal range. All the patients were screened for hepatitis B (HBsAg). None of our patients had hepatitis B.

Liver and cardiac iron concentration measurement

All the patients were subjected to MRI examination on 3.0-T MRI (Discovery 740W GE, Ohio, WI, USA). Multiecho T2* MRI (TE = min, TR = 30 ms, frequency FOV = 42 cm, phase FOV = 0.8 cm, slice thickness = 8 mm, spacing = 15 mm, flip angle = 25°, frequency direction = R/L, NEX = 1) of the entire liver was performed.

ROI was placed in three areas with maximum signal change, and an average T2* value was obtained (Fig. 1). Major vessels of the liver were avoided while placing ROI. Similarly, a single ROI was placed at the mid-interventricular septum in the heart on a short-axis view, and a T2* value was obtained (Fig. 2). T2* values so obtained were converted to iron concentration with the help of a T2* iron concentration calculator (available as freely downloadable software).

LIC was calculated in all 51 patients while CIC was calculated in 48 patients.

Serum ferritin measurement

MRI examination was done within 5 days of blood transfusion. Blood sample was taken from each patient within 15 days of MRI examination, and serum ferritin concentration was obtained by ELISA technique using a standard Calbiotech, ferritin SA ELISA kit to evaluate iron overload.

A blood specimen was collected, and the serum was separated immediately by centrifugation method. The serum was stored at 2–8 °C for the duration (not more than 30 days) before the ferritin analysis was done. Using the reagent provided in the kit, the ELISA test was first performed in the six ferritin standards (concentrations of these standards were known) which were available in the ferritin kit, and their absorbance values were noted at 450 nm optical density (OD) (Table 1).

A standard concentration curve was then drawn by plotting the absorbance value at OD 450 nm (horizontal axis) versus the concentration of six ferritin standards (already known) (vertical axis) as shown in Fig. 1, and the value for each sample was calculated using the standard curve (Fig. 3). The liver iron values were correlated with serum ferritin value.

Statistical analysis

Numerical data was expressed as mean ± 2 standard deviations. The Spearman correlation test was used to correlate the T2* value of the liver with liver iron concentration and serum ferritin, liver iron concentration with serum ferritin, T2* value of the heart with cardiac iron concentration and serum ferritin, cardiac iron concentration with serum ferritin and T2* values of the liver and

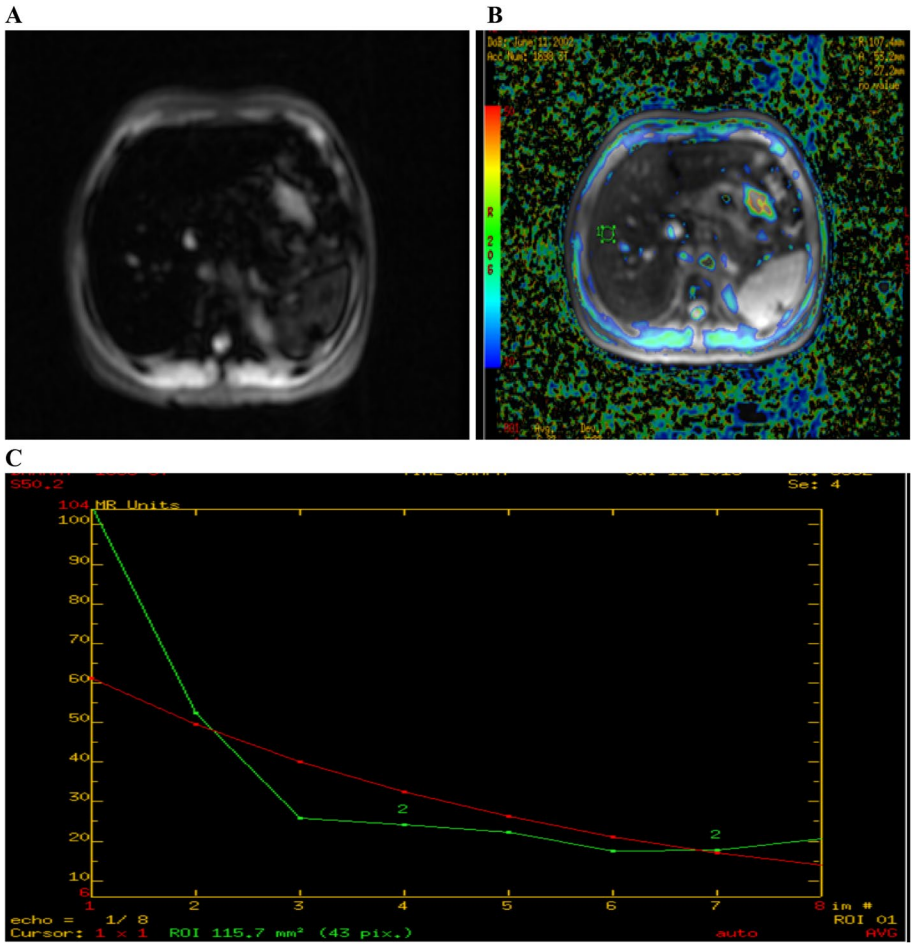

Fig. 1 **A**, **B** Greyscale T2*W and corresponding colour-coded axial image of the liver showing ROI with a T2* value of 6.33 ms, corresponding LIC being 2.6 mg/g. **C** T2 decay graph in the region of ROI in the liver

heart. A two-sided p value < 0.01 was regarded as statistically significant. Statistical analysis was performed using IBM SPSS Statistics V22.0.

Results

Out of 51 patients studied for liver iron concentration, 4 showed normal iron levels, 45 had mild iron deposition, 2 had moderate and none had severe iron deposition. Of the 48 patients studied for cardiac iron concentration, 45 were normal, 3 had mild to moderate iron deposition and none had severe iron deposition. The reference range for liver and cardiac iron concentrations along with the number of cases is shown in Table 2.

The mean T2* value for the liver in the study group was 5.63 ± 2.38 ms, and the range was 2.2–12.9 ms. The mean LIC was 3.38 ± 1.36 mg/g dry weight, and the range was 1.30–7.30 mg/g dry weight.

There was a strong negative correlation between the T2* value of the liver and LIC with a correlation coefficient − 0.895 (p value < 0.01) (Fig. 4), a negative correlation between T2* value of the liver and serum ferritin with a correlation coefficient of − 0.636 (p value < 0.01) and a positive correlation between LIC and serum ferritin with a correlation coefficient of 0.642 (p value < 0.01) which is moderately significant.

The mean T2* value of the heart obtained at the mid-interventricular septum of 48 patients was 33 ± 16.5 ms, and the range was from 8.3 to 78.8 ms. The mean cardiac iron concentration was 0.61 ± 0.31 mg/g dry weight, the and range was 0.30–1.80 mg/g dry weight.

There was a strong negative correlation between the T2* value of the heart and CIC with a correlation coefficient of − 0.959 (p value < 0.01) (Fig. 5). There was no correlation between the T2* value of the heart and serum ferritin with a correlation coefficient of 0.135 (p value = 0.359). There was no correlation between CIC and serum ferritin with a correlation coefficient of − 0.137 (p value = 0.354).

Serum ferritin of all 51 patients was obtained. The mean serum ferritin level in the study group was 1871 ± 594 ng/

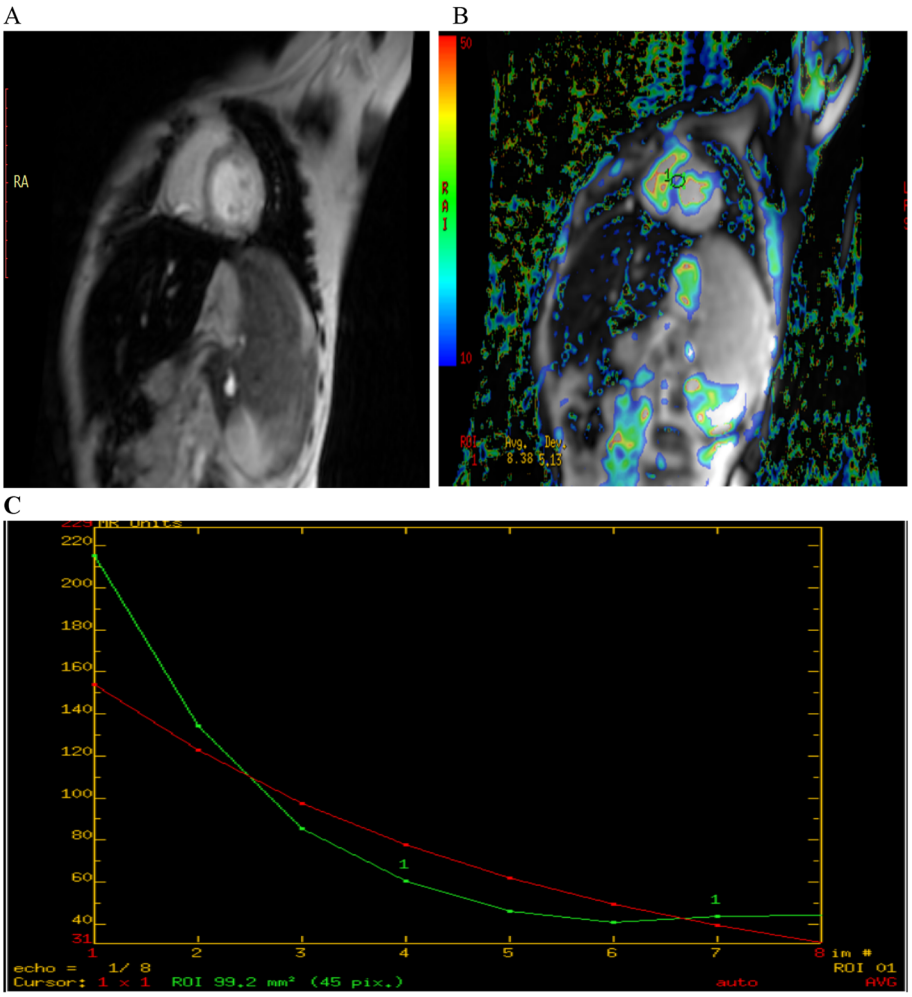

Fig. 2 **A**, **B** Greyscale T2*W and corresponding colour-coded image of the heart showing ROI in interventricular septum with a T2* value of 8.38 ms, corresponding CIC being 1.8 mg/g. **C** T2 decay graph in the region of ROI in the heart

Table 1 Absorbance values at OD 450 nm and concentration of six ferritin standards

	Absorbance at OD 450 nm (AU)	Concentration (ng/ml)
Standard 1	0.009	0
Standard 2	0.152	10
Standard 3	0.632	50
Standard 4	1.308	150
Standard 5	2.0005	400
Standard 6	2.412	800

dl, and the range was 1028–3205 ng/dl. T2* values show a strong negative correlation with iron concentration in the case of both the liver and heart. So, MRI is a powerful non-invasive tool to calculate iron concentration and titrate chelating agents accordingly. There was no correlation between T2* values of the liver and heart with a correlation coefficient of 0.051 (p value 0.365).

These results show that T2* values as calculated on the T2* multiecho sequence of MRI very accurately predict both liver and cardiac iron concentration, while serum ferritin levels only moderately predict liver iron concentration and cannot accurately determine cardiac iron concentration. Hence, MRI is a better tool to titrate the doses of chelating agents as it is accurate, non-invasive, does not involve radiation hazards and can be repeated as and when needed. Moreover, the iron load in the liver also does not give an idea about the iron load of the heart. Hence, it is a better idea to image the heart along with the liver (it is a comparatively short sequence and does not add much to scanning time) as both liver iron level and serum ferritin do not predict cardiac iron status which is important to assess as cardiac overload can lead to fatal heart problems.

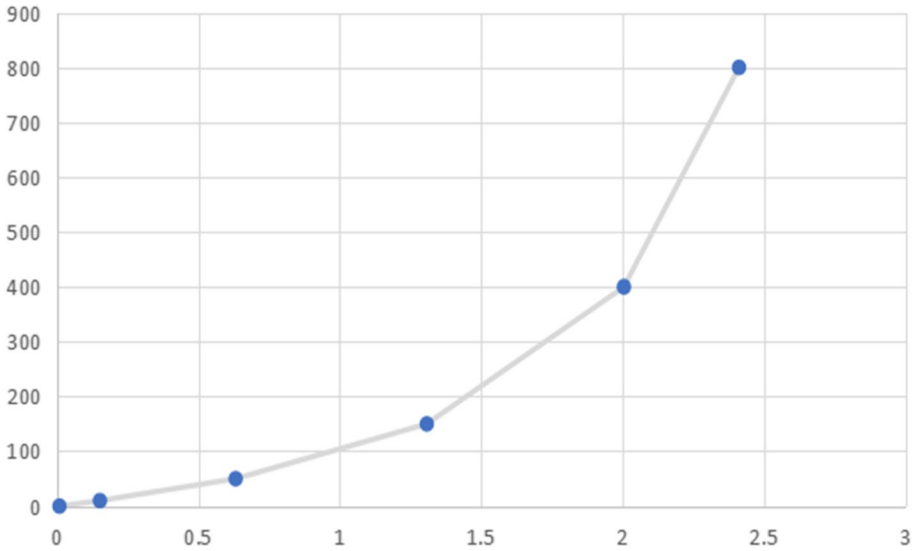

Fig. 3 Standard concentration curve of six standard ferritin reagents

Table 2 Reference range for T2* value and iron concentration for mild, moderate and severe cases of liver and cardiac iron overload and number of patients falling in each category

Organ	Severity of iron deposition	T2* (ms)	Iron concentration (mg/g)	Number of cases
Liver	Normal	> 8.4	< 2.0	4
	Mild	2.3–8.4	2.0–7.0	45
	Moderate	1.05–2.3	7.0–15	2
	Severe	< 1.05	> 15	0
Heart	Normal	> 12.6	< 1.16	45
	Mild to moderate	5.8–12.6	1.16–2.71	3
	Severe	< 5.8	> 2.71	0

Discussion

The majority of our patients (88.2%) had mild iron deposition in the liver. Only 3.9% had moderate iron deposition while none had severe iron deposition. This may be because all our patients were under institutional care and already receiving chelation therapy. Out of 48 patients imaged for cardiac iron, 93.7% were normal, 6.3% had mild to moderate cardiac iron deposition and none had severe iron deposition. Wahidiyat et al. [6] found that 85.2% of the subjects had normal cardiac iron stores while 70.4% of the subjects had severe liver iron overload.

Suthar et al. [7] found a negative correlation between serum ferritin and T2* value of the liver ($r = -0.448$, $p < 0.01$), but no correlation was found between serum ferritin and T2* value of the heart ($r = -0.221$, $p = 0.060$). We also observed a negative correlation between serum ferritin and T2* value of the liver ($r = -0.636$. $p = < 0.01$), but no correlation was seen between the T2* value of the heart and serum ferritin ($r = 0.135$, $p = 0.359$). Our study correlates well with Suthar et al.'s [7] study but showed a slightly stronger negative correlation between serum ferritin and liver T2* value (−0.636 vs −0.448). Leung et al. [8] also found an inverse correlation between liver T2* value and both current and 12-month average serum ferritin ($r = -0.44$, $p = 0.003$; $r = -0.46$, $p = 0.002$). Zamani et al. [9] found a moderate negative correlation between serum ferritin levels and liver MRI T2* values ($r = -0.586$, $p = 0.000$). Mandal et al. found [10] a moderate correlation between LIC and serum ferritin levels ($r = 0.522$; $p < 0.001$). Wahidiyat et al. showed a slight correlation ($r = 0.37$) between LIC and serum ferritin [6]. Angulo et al.'s [11] retrospective study, however, showed no correlation between mean ferritin and LIC.

Similar to our study, most of the previous studies like those of Leung et al. [8] also failed to correlate serum ferritin level and T2* value of heart except for the study by Azarkeivan et al. [12] ($r = -0.361$) and Wahidiyat et al. [6] ($r = -0.28$) who showed poor negative correlation between the two. Mandal et al. [10] showed a slight positive correlation between CIC and serum ferritin ($r = 0.483$).

In fact, most of the studies have shown the same trend, weak correlation between liver iron concentration and serum ferritin and no correlation between cardiac iron concentration and serum ferritin. This may be because though acceptable for clinical purposes, the value of

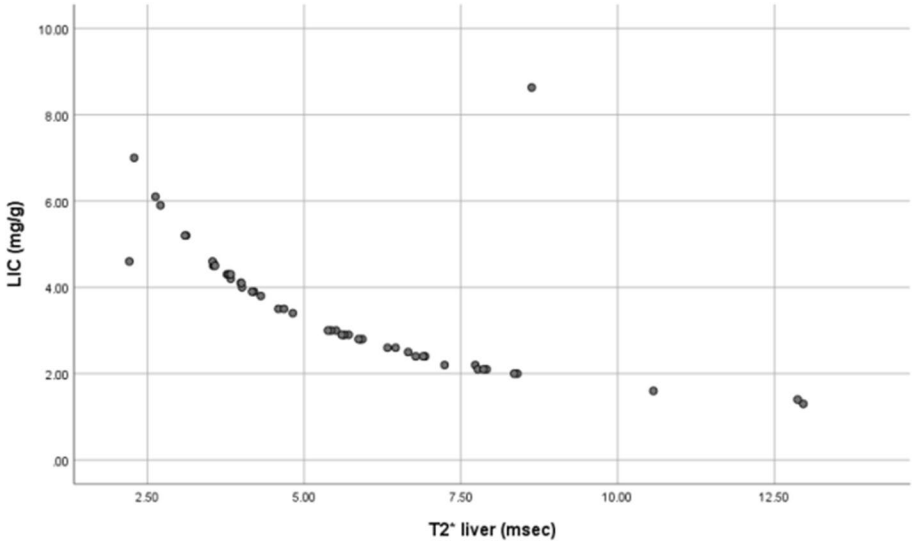

Fig. 4 The scatter dot chart showing a negative correlation between the T2* value of the liver and liver iron concentration

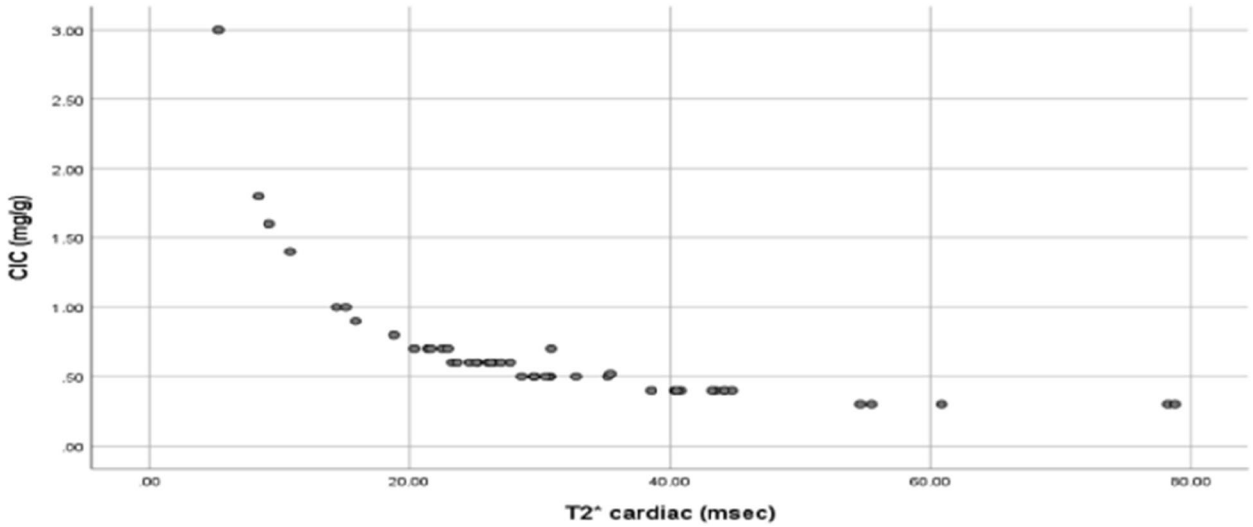

Fig. 5 The scatter dot chart showing a negative correlation between T2* cardiac and cardiac iron concentration

cardiac iron concentration as measured by T2*W imaging is less reliable than that of the liver due to two regions, first is susceptibility artefacts due to interface with air in the lungs and second due to continuous cardiac motion. This susceptibility effect is more prominent in the 3.0-T system as compared to the 1.5-T system. Moreover, the TE value cannot be reduced beyond a certain limit in case of cardiac imaging to accommodate for cardiac gating. This also affects the results.

Kolnagou et al. [13] observed that serum ferritin correlated with T2* of the spleen ($r=-0.81$), liver ($r=-0.63$) and pancreas ($r=-0.33$) but not with the heart. A similar trend was observed in the correlation of liver T2* with the T2* of the spleen ($r=0.62$) and pancreas ($r=0.61$) and none with the heart. These studies contradict previous assumptions that serum ferritin and liver iron concentration is proportional to the total body iron stores in thalassemia and especially cardiac iron load. Previously, it was thought that the liver being the largest storage site of iron, if overloaded, will proportionately affect the organs such as the heart also. However, we failed to correlate these two parameters. The correlation coefficient between T2* values of the liver and heart in our study was $r=0.051$ with a probability of 0.365 both

of which are insignificant. Our results are consistent with the findings of Kolnagou et al. [13] and Azarkeivan et al. [12]. Azarkeivan et al. [12] observed that the correlation coefficient between T2* liver and heart was 0.281, which is insignificant.

Voskaridou et al. [14] showed that heart T2* values correlated with left ventricular ejection fraction in thalassemia major, but further suggested that results of T2 relaxation for the heart become reliable only when there is heavy iron deposition. Carpenter et al. studied the role of T2* magnetic resonance in monitoring iron chelation therapy. They suggested that the lowest values of myocardial T2 * < 10 ms predict a high risk of the development of cardiac failure ($p < 0.001$). Analysis of T2* revealed an increasing risk of developing heart failure with progressively lower T2* values with the greatest risk in patients with T2* < 6 ms. It can be used to monitor chelation, allowing individually tailored chelation therapy to improve outcomes and prevent cardiovascular complications [15]. In our study, three patients had mild to moderate cardiac iron deposition. One was a 14-year-old girl who had mild LIC and normal CIC when first scanned, but then she defaulted on chelation therapy. A repeat MRI done 6 months later showed mild LIC, but now, there was mild to moderate CIC (1.4 mg/g) also with cardiac T2* value of 10.81 ms, and her ejection fraction was 45%. She developed septicemia also and succumbed (though her cardiac iron was mild to moderate, the already compromised heart probably could not tolerate the stress of septicemia). During this 6-month period, her serum ferritin shot from 1119 to 10,000 ng/ml, which could be due to a combination of increased body iron (due to default on chelation therapy) as well as due to inflammation associated with septicemia. Two boys (aged 17 and 12 years) also had mild to moderate cardiac iron deposition (1.6 mg/g and 1.8 mg/g, respectively). The dose of chelation was increased for both the boys, and both are doing fine now (previously, both were on oral deferasirox 30 mg/kg OD, after cardiac involvement was found on MRI, desferrioxamine subcutaneous was added).

Casale et al. [15] suggested serum ferritin ≥ 2000 ng/ml and liver iron concentration ≥ 14 mg/g/dry weight as the best threshold for predicting cardiac and hepatic iron overload ($p = 0.001$ and $p < 0.0001$, respectively). A homogeneous pattern of myocardial iron overload was associated with negative cardiac remodelling and significantly higher liver iron concentration ($p < 0.0001$). Myocardial fibrosis by late gadolinium enhancement was detected in 15.8% of the patients [15]. We, however, could not find late gadolinium enhancement probably because the patients had only mild to moderate CIC, and as they were under institutional care, titration of chelation was immediately done. The only girl child who deteriorated was dead before a detailed workup could be done. Even the threshold of ≥ 2000 ng/ml ferritin for cardiac iron overload did not hold true in our study. All three patients with cardiac iron deposition had serum ferritin well below 2000 ng/ml.

There are some important technical points which need to be kept in mind while measuring liver/cardiac iron concentration using T2*W imaging. TE needs to be minimum (the first echo should preferably be < 1 ms on the 1.5-T system and < 0.5 ms on the 3.0-T system). If the organ iron load is high, it may give fallacious readings or no values. In such conditions, try to minimise the TE. This can be achieved by decreasing frequency or increasing bandwidth. Even after these corrections, if the values seem to be doubtful, a three-parametric fitting algorithm should be used instead of the default two-parametric fitting algorithm. The greyscale images of the multiecho sequence should always be analysed before calculating the T2* value/LIC. This will help in identifying false lower values of iron in cases of heavy iron load. The first two images of the multiecho sequence should have at least some liver signal. The collapse of signal in the first few images of the multiecho sequence is an indicator of heavy iron overload and such patients should be rescanned with parameter modification as described (Fig. 6). Another way to take care of fallacious values in severe iron load is to take the ratio of signal intensities of liver and paraspinal muscles, but for this, a body coil should always be used and not surface coil. The two methods (T2* value-based LIC and the ratio of signal intensities of liver and paraspinal muscles) can, in fact, be used together also. It is important to standardise the method used and stick to that particular method in follow-up examinations.

This study faced some limitations, single measurement of serum ferritin which was done within 15 days of MRI examination. An average value of the last 6-month ferritin level might have reflected the true status, but some of the recent studies also have used a single measurement of serum ferritin [14]. Interpretation of serum ferritin values may be confounded by a variety of conditions that alter serum ferritin concentrations independently of changes in the body's iron burden including vitamin C deficiency, fever, acute and chronic hepatic damage, hemolysis and ineffective erythropoiesis; all of which are common in patients with b-thalassemia major [3]. Fatty infiltration of the liver may also affect the T2* and hence liver iron concentration values.

Out of the 51 cases, 4 cases showed normal T2* values of the liver despite moderately high serum ferritin concentration. These variable results could be because of the differences in clinical, genetic and demographic characteristics of the study population such as age, sample size,

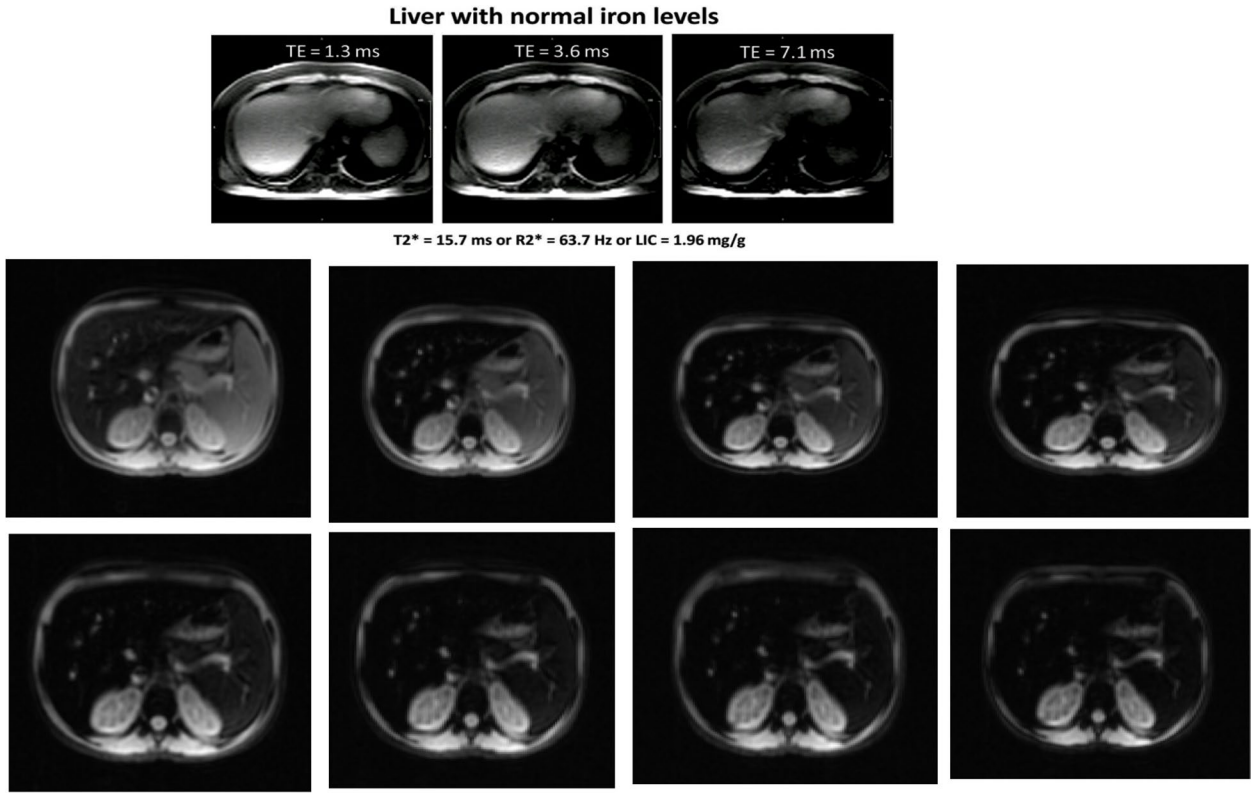

Fig. 6 T2* images representing a normal (upper row) and severely iron-overloaded liver (lower row). In the normal liver, the signal intensity does not change significantly as the echo times (TEs) increase. In comparison, a severely overloaded liver is dark even at TE of 1.3 ms and completely black in the subsequent TEs

serum ferritin levels, chelating protocols and iron kinetics of different organs.

To conclude, MRI is the most sensitive and specific imaging modality in the diagnosis of parenchymal iron overload in thalassemia patients on regular blood transfusion. The susceptibility effect caused by the accumulation of iron leads to signal loss in the affected tissues, particularly with the T2*-weighted sequences, which makes the diagnosis of iron overload possible in a non-invasive way, thereby avoiding repeated biopsies [5]. As the involvement of the heart and liver are the major determinants of mortality in thalassemia, these organs need to be screened regularly for iron deposition during chelation therapy. Now, MRI-based organ assessment is considered the gold standard and should be used for assessing iron concentrations in various organs mainly the liver and heart.

Conclusions

MRI is a useful tool to titrate the doses of chelating agents as it is accurate, non-invasive, does not involve radiation hazard and hence can be repeated as and when needed. Simultaneous assessment of cardiac iron overload is an added advantage of MRI.

Abbreviations

MRI	Magnetic resonance imaging
SF	Serum ferritin
LIC	Liver iron concentration
CIC	Cardiac iron concentration
OD	Optical density
ELISA	Enzyme-linked immunosorbent assay

Acknowledgements

Not applicable.

Authors' contributions

SR, KSC, DS and AV contributed equally to this work. SR and KSC designed the research. KSC performed the research. SR, AV, AY and PSG analysed the data. SR and DS wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All the datasets used and analysed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the research ethics committee of the Pt B D Sharma PGIMS, Rohtak on 28/02/2019 (reference number of approval: BREC/Th/18/Radiology/01). All patients included in this study gave a written informed consent to participate in the research.

Consent for publication
All patients included in this study gave a written informed consent to publish the data contained in this study.

Competing interests
The authors declare that they have no competing interests.

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