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# Role of cardiac magnetic resonance T1 mapping in comparison to T2\* for cardiac iron overload assessment in transfusion-dependent thalassemia major patients

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## Abstract

**Background** Cardiac complications are the leading cause of death in transfusion-dependent thalassemia major (TDT) patients due to increased cardiac iron overload (CIO), so this study's purpose is to assess the diagnostic utility of cardiac magnetic resonance T1 mapping in correlation to T2\* for the assessment of CIO in TDT patients. This prospective case–control study involved 55 TDT patients and 30 age- and gender-matched healthy controls. All the patients underwent assessment of myocardial T2\*, and native T1 values by conventional cardiac magnetic resonance imaging, and native T1 mapping technique to assess the CIO. Comparison and association between T2\*, and native T1 values among TDT patients were studied.

**Results** A statistically significant difference is noted between control and patient groups in regard to mean T2\* and native T1 values ( $P=0.03$  and  $0.01$ , respectively). The mean native T1 value in TDT patients was lower than in the control group ( $992 \pm 54$  vs.  $1234 \pm 42$ ), respectively, with a statistically significant  $P$  value of  $0.04$ . The study evoked a statistically significant strong positive association, and correlation was noted between measured T2\* and native T1 values ( $r=0.84$ ,  $P$  value =  $0.001$ ), while a moderate negative association was observed between native T1 values and S. ferritin levels ( $r=-0.53$ ,  $P$  value =  $0.02$ ).

**Conclusions** Native T1 mapping is a non-invasive promising complementary technique to T2\* that helps to detect cardiac iron overload in TDT patients, as it is strongly associated with T2\*. Also, native T1 value can differentiate mild, moderate, severe, and no cardiac iron overload.

**Keywords** Cardiac magnetic resonance, Iron overload, T1 mapping, T2\*, Thalassemia

## Background

Thalassemia is a hereditary gene disorder resulting in abnormal hemoglobin synthesis and hemolytic anemia, which is common among the Mediterranean populations [1]. Thalassemia major is the most serious type, in

which patients have chronic hemolytic anemia and need prolonged transfusion therapy, which results in increased tissue iron overload.

Cardiac complications due to increased myocardial iron overload with subsequent cardiomyopathy and heart failure are the leading cause of increased morbidity and mortality among these patients [2]. So, iron chelation therapy is introduced at an early age in order to decrease the risk of mortality among thalassemia patients and should be suitable for individual patient needs [2, 3]. Thus, assessment of myocardial iron overload

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is mandatory for chelation therapy and follow-up of response [3, 4].

Cardiac magnetic resonance (CMR) is used for the quantification of myocardial iron overload as the only non-invasive technique. That myocardial iron deposition leads to magnetic field homogeneities which results in decreased T1, T2, and T2\* relaxation times [5–7].

The T2\* technique is the sequence of choice for myocardial iron quantification and becomes a reference tool according to the clinical guidelines. It has a prognostic role, in that it allows detection of heart failure risks and the need for chelation therapy [8–11]. Although it is a fast and reproducible technique, it has some limitations as its sensitivity to the susceptibility artifacts and decreased sensitivity in mild or early myocardial iron overload (MIO) [12]. The native myocardial T1 mapping may be a promising technique that overcomes this limitation [12–14].

The native T1 mapping permits a non-invasive assessment of myocardial edema, and accumulation of T1 altering substances including iron without the need for gadolinium-based contrast studies. It can demonstrate a progressive decrease in native T1 through the spectrum of myocardial iron load [3, 15–17].

So, the aim of this study is to assess the diagnostic utility of cardiac magnetic resonance T1 mapping in correlation to T2\* for the assessment of cardiac iron overload in transfusion-dependent thalassemia major (TDT) patients.

## Methods

A prospective descriptive analytical case–control study was approved by the local institutional ethics committee with obtained signed written informed consent from all study participants.

### Study populations

This prospective case–control study involved 55 patients with beta-thalassemia major and 30 age- and gender-matched healthy volunteers as control subjects. The study was performed from January 2022 to June 2023.

*Inclusion criteria of the patient group* involved: (a) Male and female patients older than 5 years old diagnosed with beta-thalassemia major according to the Thalassemia Clinical Research Network guidelines concerning the clinical, laboratory, and hematological findings [18] and (b) patients on regular blood transfusion (every 2–4 weeks). *The control group included* male and female healthy volunteers with matched ages and gender.

Meanwhile, the *exclusion criteria* included: (a) patients with other types of thalassemia (alpha, minor, and intermedia), (b) the presence of other chronic diseases such as diabetes mellitus and renal or cardiac disease, (c) history

of previous traumatic or cardiac surgery, (d) patients with vascular, immunological, or neoplastic disease, and (e) patients with MRI absolute contraindications and MRI claustrophobia.

All participants underwent history taking, and cardiac magnetic resonance imaging including T2\* and T1 (MOLLI) sequences, as the following:

### History taking and basic data

Patient's age, gender, disease duration, history of blood transfusion, and iron chelation therapy.

### Laboratory investigation

Laboratory data were obtained from the TDT patients; S. hemoglobin, S. iron, and serum ferritin levels.

### Cardiac magnetic resonance examination

All patients underwent cardiac magnetic resonance imaging (CMR) T2\* and T1 mapping; with CMR-derived T2\* calculated value is the gold standard.

### Cardiac magnetic resonance scan

The imaging scan was performed using a 1.5-Tesla MR scanner (Philips Medical Systems, Achieva 1.5-T A-series). MRI findings were interpreted by two radiologists of 10 years experience in cardiac MRI and were blinded to patient clinical and laboratory data.

### Cardiac MRI sequences

(A) Basic conventional cardiac magnetic resonance imaging to obtain morphological and function information in the form of single breath-hold multi-gradient-echo sequences, (a) localizer images in axial, coronal, and sagittal orthogonal dimensions, (b) left anterior oblique (LAO) view, (c) four-chamber view, and (d) cardiac bright blood (mTFE) short axis.

#### (b) T2\* CMR

It is a single breath-hold bright blood gradient-echo sequence for myocardial T2\* values measurement. Data acquisition involved segmented and non-segmented single breath-hold gradient-echo pulse sequences with a readout for a range of respective echo times. Eight echoes were acquired for the assessment of myocardial T2\* relaxation time. Mid-ventricular short-axis slices were used for the T2\* measurement of the myocardium. T2\* images were obtained by utilizing the following parameters (TEs: 1.5–17.3 ms, TR: 710 ms, slice thickness: 10 mm, flip angle: 20°, FOV: 400×300 mm, matrix: 256×96, and bandwidth: 810 Hz/Px).

#### (c) Myocardial non-contrast T1 mapping

It is a balanced steady-state free precession (SSFP) and single breath-hold modified inversion recovery Look-Locker sequence (MOLLI). The data acquisition period is

of five heartbeats that are followed by a recovery period of three heartbeats and then another data acquisition period of three heartbeats; the image acquisition algorithm was 5(3) 3 in the apical, mid-ventricular, and basal short-axis slices. It was done according to previously reported in Taylor et al. [16].

#### Post-processing of cardiac magnetic resonance images

(A) For  $T_2^*$  assessment of myocardial iron overload: The corresponding image raw data were processed by a dedicated Philips workstation (Cardiac Analysis Workflow, Philips Medical Systems, Achieva), CMR Tools software for  $T_2^*$  values determination and estimation by utilizing a fitting robust technique through the fitting of images signal intensities to the  $T_2^*$  decay model. Normal cardiac iron was considered to be  $>20$  ms. While, cardiac iron overload (CIO) was defined as a  $T_2^*$  of  $<20$  ms and is graded as the following (mild CIO as 15–20 ms, moderate CIO as 10–15 ms, while severe cardiac iron overload (CIO) as a  $T_2^* < 10$  ms).

(b) For  $T_1$  mapping assessment of myocardial iron overload: A total of eight images were acquired with different inversion times (TI) via 11 heartbeats. Non-contrast native  $T_1$  value quantification was performed by using the dedicated standard software on a Philips Medical System workstation (extended workspace) using the cardiac explorer program, and CVI42 post-processing program dedicated to the research work. A semiautomatic tracing of both epicardial and endocardial contours of the region of interest was done at mid-ventricular, basal, and apical short-axis slices. Automatic calculation of the average global myocardial native  $T_1$  values was done (Figs. 1, 2, 3, 4, and 5).

#### Statistical analysis

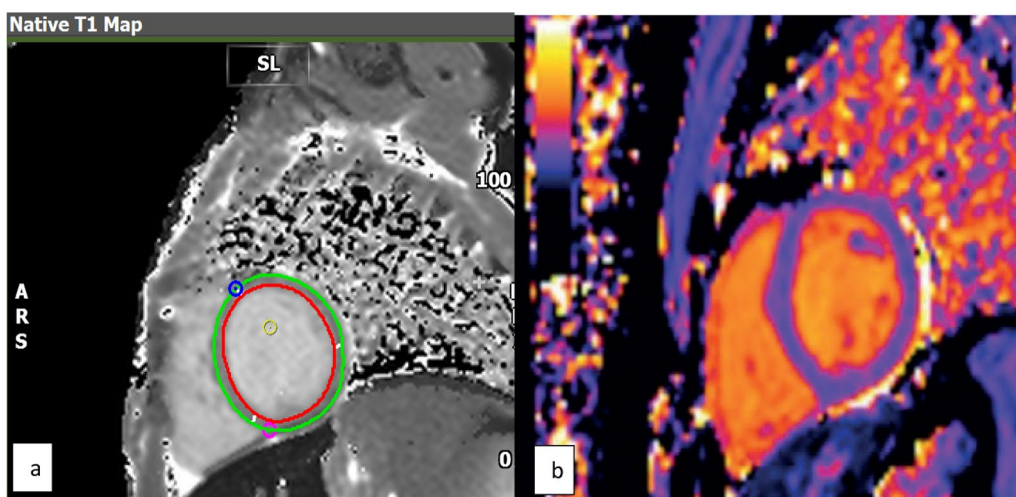
All analyses were performed using a Statistical Package for the Social Sciences (SPSS) Windows version 22.0 (IBM Corporation, Armonk, New York). Shapiro–Wilk or Kolmogorov–Smirnov tests were used to test the normality of the collected data. The numerical or quantitative data were presented as mean  $\pm$  SD, while the categorical data were recorded as numbers and percentages. The Mann–Whitney test was used for the analysis of non-parametric data. Analysis of variance was used for comparison between parametric data. Tests for association analysis such as Pearson's association analysis were utilized. The intraclass correlation coefficient was calculated through obtained the two-way random effects model with absolute agreement measures, also the Bland–Altman test was utilized to obtain the absolute difference against the average values between the two datasets.

Comparison of the continuous data was done by employing unpaired Student's *t*-tests or one-way analysis of variance for between-group comparisons. Non-normally distributed continuous variables were compared by Wilcoxon signed-rank or Kruskal–Wallis tests. The *P* value was considered significant if  $<0.05$ .

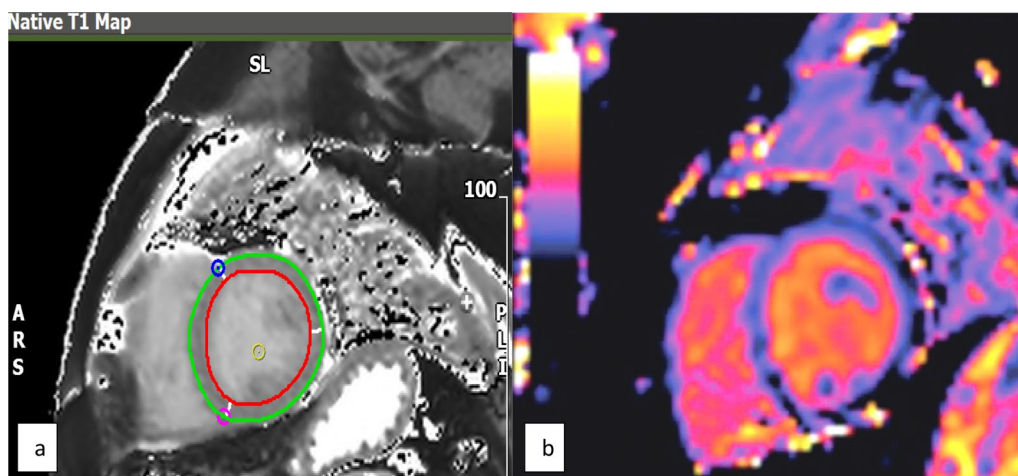
#### Results

This study included 55 TDT patients (21 females and 34 males, with the age range of 7–19 years, mean age 8.3 years) and 30 age- and gender-matched controls (four females and 16 males, mean age 8.5 years, age range 8–20 years).

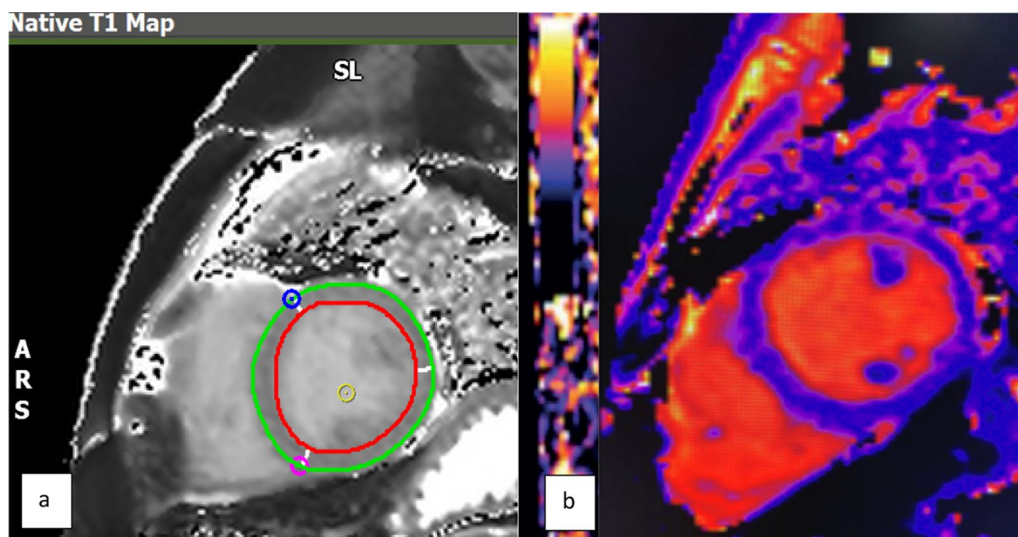
The demographic, clinical parameters, laboratory data (serum hemoglobin, serum, iron, and serum ferritin), and types of used iron chelation therapies are



**Fig. 1** Cardiac magnetic resonance: **a** mid-ventricular short-axis native  $T_1$  and **b** mid-ventricular short-axis native  $T_1$  color map in a 15-year-old male healthy volunteer ( $T_2^* = 39$  ms, global native  $T_1 = 1592$  ms)



**Fig. 2** Cardiac magnetic resonance: **a** mid-ventricular short-axis native T1 and **b** mid-ventricular short-axis native T1 color map in an 8-year-old female patient with beta-thalassemia major with mild myocardial iron overload ( $T2^* = 18$  ms, global native T1 = 997 ms)



**Fig. 3** Cardiac magnetic resonance: **a** mid-ventricular short-axis native T1 **b** mid-ventricular short-axis native T1 color map in a 10-year-old male patient with beta-thalassemia major without myocardial iron overload ( $T2^* = 36$  ms, global native T1 = 1087 ms)

described in Table 1. All of the patients were in sinus rhythm, at the time of examination.

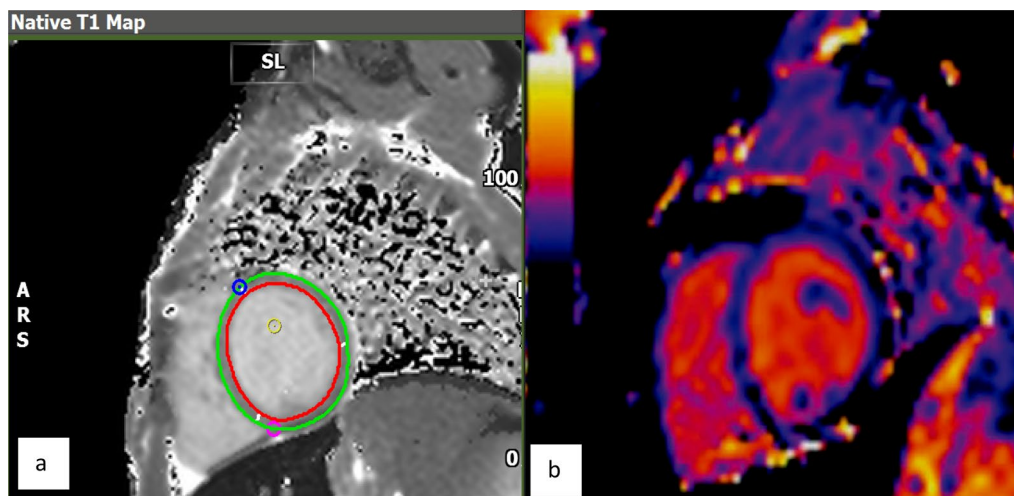
The study evoked non-statistically significant differences between the patient and control groups in regard to age, gender, and body mass index. The disease duration in the TDT was of 2–18 years, with an average disease duration of 6.3 years.

On the basis of  $T2^*$  values, there were 25 patients (45.5%) with no CIO, 22 patients (40%) with mild-to-moderate CIO, and 8 patients with severe CIO (14.5%).

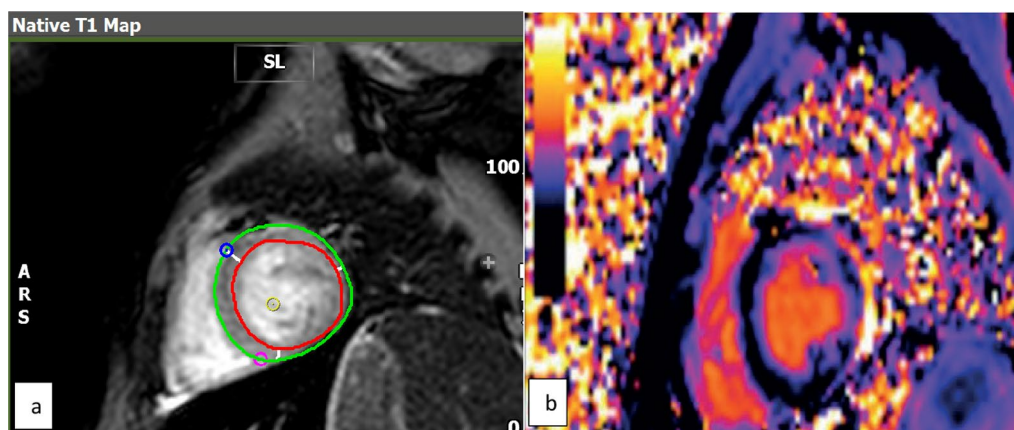
**Comparison between  $T2^*$  and native T1 values in regard to cardiac iron overload detection in blood transfusion-dependent beta-thalassemia major patients and controls**

A statistically significant difference is noted between control and patient groups in regard to mean  $T2^*$  and native T1 values ( $P = 0.03$  and  $0.01$ , respectively). Both native T1 and  $T2^*$  values were lowered in TDT patients in comparison with control group, as described in Table 2. The mean native T1 value in TDT patients was lower than in





**Fig. 4** Cardiac magnetic resonance: **a** mid-ventricular short-axis native T1 **b** mid-ventricular short-axis native T1 color map in a 13-year-old male patient with beta-thalassemia major with moderate myocardial iron overload ( $T2^* = 14$  ms, global native T1 = 886 ms)



**Fig. 5** Cardiac magnetic resonance: **a** mid-ventricular short-axis native T1 **b** mid-ventricular short-axis native T1 color map in a 14-year-old male patient with beta-thalassemia major with severe myocardial iron overload ( $T2^* = 7$  ms, global native T1 = 688 ms)

the control group ( $992 \pm 54$  vs.  $1398 \pm 112$ ), respectively, with a statistically significant  $P$  value of 0.04. The mean native T1 value in TDT with no cardiac iron overload patients was lower than in the control group ( $1165 \pm 72$  vs.  $1398 \pm 112$ ), respectively, with a statistically significant  $P$  value of 0.01.

#### Association between myocardial mean values $T2^*$ and native T1 in regard to cardiac iron overload detection in blood transfusion-dependent beta-thalassemia major patients

The study evoked a statistically significant strong positive association, and correlation was noted between measured  $T2^*$  and native T1 values ( $P$  value = 0.001) as shown in Fig. 6, while a moderate negative association

was observed between native T1 values and S. ferritin levels ( $P$  value = 0.02), as described in Table 3.

#### Association between myocardial mean values of $T2^*$ , native T1, and cardiac functional parameters in blood transfusion-dependent beta-thalassemia major patients

The study evoked a weak positive association, and correlation was noted between measured  $T2^*$  and native T1 values, and different cardiac functional parameters (ejection fraction, Lt. ventricular end-diastolic volume, and Lt. ventricular end-systolic volume), as described in Table 4.

The study revealed an excellent intra- and inter-observer agreement and consistency with a high

**Table 1** Demographic data and clinical parameters of patients and controls

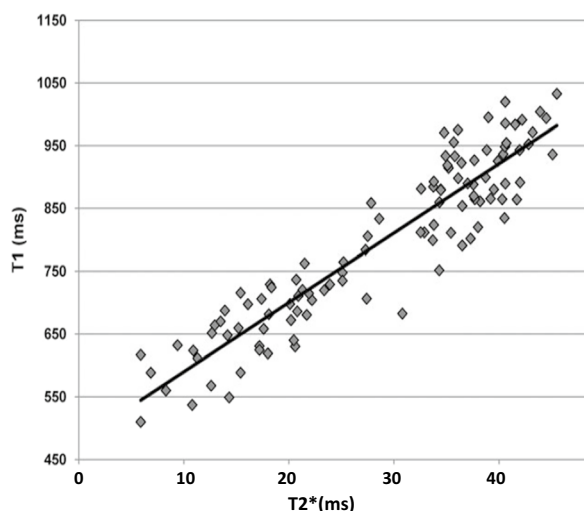
Variable	TDT patients (n = 55)	Controls (n = 30)	P value
Age	7–19 (8.3 ± 4.1)	8–20 (8.5 ± 3.8)	0.992
Height	105–160 (121.2 ± 11.5)	114–162 (128.2 ± 10.5)	0.841
Weight	16–42 (27.53 ± 4.26)	19–47 (29.59 ± 5.62)	0.794
Duration of the disease (years)		–	–
Iron chelation therapy			
Deferoxamine monotherapy (SC, IV)	9 (16.3%)	–	
Deferasirox monotherapy (Oral)	21 (38.18%)		
Deferiprone monotherapy (Oral)	17 (30.9%)		
Deferoxamine (SC,IV) and deferasirox (Oral)	8 (14.5%)		
Serum ferritin (ng/ml)	1932–6070 (2721.43 ± 815.17)	–	–
Hb level (gm/dl)	7.1–10.4 (8.1 ± 1.3)	–	–
Serum iron (mcg/dl)	654–1220 (798.64 ± 271.56)	–	–

\*Data are presented as range (mean ± SD) and percentage  
Significant P value is < 0.05

**Table 2** Comparison of mean values of T2\* and native T1 between controls versus TDT patients

Variable	T2* value (ms)	Native T1 value (ms)
Control (n = 30)	41 ± 9.6	1398 ± 112
TDT patients without CIO (n = 20)	35.2 ± 6.8	1165 ± 72
TDT patients with mild CIO (n = 15)	17.6 ± 2.1	899 ± 82
TDT patients with moderate CIO (n = 12)	12.6 ± 2.4	743 ± 72
TDT patients with severe CIO (n = 8)	6.4 ± 3.3	607 ± 79
P value	0.03*	0.01*

CIO cardiac iron overload and TDT transfusion-dependent thalassemia  
\*P value < 0.05 considered significant



**Fig. 6** Scatter plots showed a strong positive association and correlation between myocardial mean values of T2\* and native T1 ( $r = 0.84, P = 0.001$ )

**Table 3** Association of S. ferritin level and mean T2\* with mean native T1 value

	Native T1 value	P value
	r	
T2* value	0.84	0.001*
S. ferritin	–0.53	0.02*

\*P value < 0.05 considered significant

**Table 4** Association of mean T2\*, mean native T1 value, and different cardiac functional parameters

	Native T1 value		T2* value	
	r	P value	R	P value
EF	0.37	0.045*	0.29	0.042*
LVEDVI	0.32	0.106	0.27	0.213
LVESVI	0.28	0.092	0.22	0.102

EF Ejection fraction, LVEDVI Lt. ventricular end-diastolic volume indexed and LVESVI Lt. ventricular end-systolic volume

\*P value < 0.05 considered significant

**Table 5** Intra- and inter-observer agreement in T2\* and native T1 values measurements and analysis in TDT patients

	Mean difference	Limits of agreement	ICC (95% CI)
<i>Mean T2* value</i>			
Inter-observer	0.18	-1.1-2.4	0.996
Intra-observer	0.25	-1.5-1	0.975
<i>Mean native T1 value</i>			
Inter-observer	0.23	-1.5-1	0.997
Intra-observer	0.39	-3.6-4.7	0.986

ICC intraclass correlation coefficient and CI confidence interval

consistency value for T2\* and native T1 values measurements and analysis and intra-observer agreement of 0.975 and 0.986, respectively, as described in Table 5.

## Discussion

Cardiomyopathy and heart failure due to cardiac iron overload (CIO) in beta-thalassemia major patients is the leading cause of death [19]. Cardiac iron overload can be prevented by iron chelation therapy [20], which should be tailored to each patient's needs.

Cardiac magnetic resonance (CMR) is the only non-invasive technique for quantification of CIO. The T2\* technique is currently the method of choice for cardiac iron quantification to become a clinical tool and a reference method according to clinical guidelines, so, allowing the early identification of patients at risk for heart failure and needing an intensification of chelation therapy [20, 21].

The T2\* technique is fast, reproducible, and transferable among different CMR scanners, but is vulnerable to susceptibility artifacts which result in decreased sensitivity for myocardial iron detection in early or mild stages [19-23]. Recently, myocardial T1 mapping had been supposed to be a new possible approach to overcome this limitation [19-23].

Few studies [3, 5, 6, 17] were done to investigate the utility of T1 mapping and native T1 values in the detection of CIO as a new adjuvant technique that may help in improving the accuracy of cardiac iron detection and subsequently decrease the health burden in TDT patients.

Our study results showed decreased mean native T1 value in TDT patients in comparison with previously reported normal values of native T1 in the previous literature, as in [11-14].

Also, our study results are matched with the trend of decreased mean values of native T1 in TDT patients versus the healthy controls and revealed comparable results with that observed and recorded by the

previous studies. We agreed with Wing-Shan et al. [3], who recorded a decreased mean native T1 value ( $947.1 \pm 84.8$  ms) with a statistically significant  $P$  value  $< 0.05$ . Also, a study by Feng et al. [5] recorded a lowered mean value of native T1 in TDT patients (800 ms). Meanwhile, Sado et al. [6] found that the mean native T1 value of 904 ms is a good cut-off point in differentiating TDT patients and healthy controls.

Our results also agreed with results obtained from a study by Krittayaphong et al. [17] which investigates cardiac magnetic resonance (CMR) T1 and T2 mapping diagnostic performance for the assessment of cardiac iron overload (CIO) in patients with beta-thalassemia. They found that native T1 times were significantly different between patients with no CIO, mild-to-moderate CIO, and severe CIO as  $1012.7 \pm 57.7$ ,  $846.4 \pm 34.4$ , and  $601.3 \pm 34.6$  ms, respectively, and  $P$  value  $< 0.05$ .

Our study revealed a decrease in the mean native T1 value in the TDT patient group with no CIO on the basis of the T2\* value, as compared to the healthy control group.

This observation is consistent with results reported by Sado et al. [6] that about one-third of patients had lowered mean native T1 value in spite of normal T2\* value.

Another study [17] reported that 38% of TDT patients had lowered T1 values in spite of normal T2\* values. This finding implicates that native T1 values may detect early and mild myocardial iron overload.

This could be explained by T2\* needing long breath hold, so more vulnerable than T1 to susceptibility artifacts, and subsequently decreased discrimination in mild myocardial iron load [4]. Meanwhile, the native T1 mapping is less eligible for magnetic field inhomogeneity in comparison with T2\* and subsequently may be helpful when myocardial T2\* values are borderline [3, 15, 19-24].

Our study results showed a strong positive association between mean values of T2\* and native T1, a finding which is consistent and agreed with those of [3, 5, 17, 23] which demonstrate a statistically significant strong positive correlation and association between mean values of T2\* and native T1 ( $r = 0.68$ ,  $P < 0.001$ ) [5].

This finding may be related to that the detected decrease in mean values of T2\* and native T1 was owed to the microscopic magnetic field inhomogeneity caused by iron deposition in the myocardium that leads to shortened T2\* and T1 relaxation times which enables the detection of cardiac iron overload [21-23].

So, this strong association enables the usage and addition of a T1 mapping sequence in the CMR protocol concerned with the evaluation of TDT patients, as a complementary tool to T2\*, which may provide more precise reproducible serial results that help early detection of

cardiac iron overload (CIO), and follow-up after treatment by chelating agents [24, 25].

In spite of the promising results of native T1 mapping in the detection of CIO in TDT patients in comparison with the T2\* value, the small sample size is still a limitation of our study. So, further multi-center studies and investigations with larger sample sizes are important to correlate T2\* with other newly developed T1 mapping and T2 mapping techniques, demonstrating cut-off points, for more accurate and precise results that help to decrease the health burden of beta-thalassemia patients and increase the results' external validity.

## Conclusions

In conclusion, native T1 mapping is a non-invasive promising complementary technique to T2\* that helps to detect and assess cardiac iron overload in TDT patients, as it is strongly associated with T2\*. Also, native T1 value can differentiate between mild, moderate, severe, and no cardiac iron overload.

## Abbreviations

CIO	Cardiac iron overload
CMR	Cardiac magnetic resonance
MOLLI	Modified Look-Locker inversion recovery
TCRN	Thalassemia clinical research network
TDT	Transfusion-dependent $\beta$ -thalassemia major
TM	Thalassemia major

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Not applicable.

## Author contributions

HR helped in formulation of the study, preparation of methodology, data collection, analysis of the data, and writing the paper. AT helped in formulation of the study, preparation of methodology, analysis of the data, and writing the paper. The authors have read and approved the manuscript.

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## Availability of data and materials

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Approved by the local institutional ethics committee; Faculty of Medicine, Suez Canal University Health Research Ethics Board. It follows the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### Informed consent

Written informed consent was obtained from all patients and controls.

### Consent for publication

Consent for publication was obtained from the patients and controls.

### Competing interests

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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