A two-dimensional speckle-tracking echocardiography for the diagnosis of early myocardial disease in beta-thalassemia major patients

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ABSTRACT

Background	:	Although magnetic resonance imaging T2* is considered the gold standard to assess myocardial iron overload in β -thalassemia patients, its routine use is limited by the high cost and limited availability. Recent data demonstrated that strain imaging by speckle tracking is a sensitive tool for early assessment of the left ventricular myocardial dysfunction. This study aims to evaluate the clinical utility of two-dimensional (2D) speckle-tracking echocardiography (STE) for the detection of early myocardial disease in beta-thalassemia major (β -TM) patients.
Materials and Methods	:	2D STE, magnetic resonance imaging (MRI) heart T2 [*] and MRI liver iron content were done for 30 β -TM patients with no clinical heart disease, compared to 2D STE in 30 healthy age- and sex-matched controls.
Results	:	There was a significant reduction in the longitudinal systolic strain values by STE among β -TM patients compared to controls ($P < 0.05$). A longitudinal peak systolic strain cutoff values of ≤ -19 was able to detect β -TM patients having subclinical cardiac iron overload by MRI T2* (sensitivity = 90%–93.3%, specificity = 83%–100%). Mean serum ferritin in the past 2 years correlated negatively to longitudinal systolic strain values global longitudinal peak systolic strain average ($P < 0.05$).
Conclusions	:	STE techniques are an alternative method to detect early myocardial disease before clinical systolic dysfunction in β-TM patients.
Keywords	:	Beta-thalassemia, iron overload, magnetic resonance imaging, speckle-tracking echocardiography

INTRODUCTION

Multiorgan iron overload in patients with thalassemia major is a result of lifelong blood transfusions and altered iron homeostasis due to ineffective erythropoiesis.^[1] Iron cardiomyopathy is the main cause of mortality

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and morbidity among beta-thalassemia major (β -TM) patients, especially those with high myocardial iron concentrations.^[2] Many thalassemia patients remain asymptomatic until becoming decompensated, but only

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50% of the patients will survive after development of overt heart failure.^[3] Parameters such as left ventricular ejection fraction (LVEF) or fractional shortening (LVFS) by the conventional echocardiography are not sensitive enough to detect subclinical cardiac dysfunction.^[4]

Although magnetic resonance imaging (MRI) T2* is considered the standard tool to detect and monitor myocardial iron overload, its routine use is limited by its high cost and restricted availability.^[5] Recent data demonstrated that strain imaging by speckle tracking is more sensitive than the conventional echocardiography for the assessment of left ventricular (LV) myocardial function.^[6] The longitudinal strain of the LV myocardium, as a part of a its multi-dimensional deformation during the cardiac cycle, causes shortening of the LV along its longitudinal axis; the rotation of the LV apex and base in opposite directions during systole produces a twist of the LV which is important to the normal systolic function of the LV and the subsequent untwist during diastole produces a suction force that is the key mechanism driving the early diastolic filling of the LV.^[7] Through the tracking of the displacement of speckles during the cardiac cycle and the evaluation of the occurrence, direction, and velocity of left ventricle (LV) rotation, speckle-tracking echocardiography (STE) provides a quantitative assessment of global and regional myocardial function.[8,9]

In this study, our primary goal was to evaluate the clinical utility of two-dimensional (2D) STE for early detection of myocardial disease in transfusion-dependent β -TM patients and to assess its specificity and sensitivity in comparison to cardiac MRI T2* as well as its relation to iron overload state.

MATERIALS AND METHODS

This cross-sectional study included 30 β -TM patients (17 males and 13 females); recruited from the Pediatric Hematology Unit, aged more than 10 years and diagnosed by an initial high-performance liquid chromatography (HPLC) hemoglobin electrophoresis.^[10,11] Based on the American College of Cardiology/American Heart Association classification, β -TM patients with clinical heart failure^[12] were excluded from the study. Patients were compared to 30 age- and sex-matched healthy controls enrolled as controls. The mean age of the patients was 14.77 ± 2.45 years, while that of the control group was 15.33 ± 2.32 years.

Data collected from the files of the patients included: age at onset, duration of the disease, the transfusion requirement (packed red cell per body weight in kilogram per year) in the last 2 years before the study, iron chelation therapy and the assessed compliance using the patient self-report of dose-taking and by checking the prescription refill and pill count; a cutoff point below 80% was considered as poor compliance,^[13] history of splenectomy and viral hepatitis (hepatitis B and or C virus) infection. All included patients were subjected to detailed clinical and cardiac examination including blood pressure measurement and those with hypertension were excluded.

Laboratory testing included

CBC using Sysmex XT-1800i (Sysmex, Kobe, Japan), markers of hemolysis (lactate dehydrogenase [LDH] and indirect bilirubin) using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). The mean pretransfusion hemoglobin was calculated, as well as the mean serum ferritin in the last 2 years prior to the study. A cutoff serum ferritin value of 2500 ng/ml was used to classify patients into two groups: those with mean serum ferritin <2500 ng/ml in the last 2 years prior evaluation, and those with mean serum ferritin \geq 2500 ng/ml.

Transthoracic echocardiography

Echocardiography was performed by an experienced cardiologist; who was unaware of children's clinical details; using Vivid E9 (GE Healthcare, Norway) Echo systems. The images were analyzed twice by the same radiologist (1 week apart) and the same images were assessed by two different radiologists blinded to each other's results. The standard two-dimension, color flow mapping, and M-mode measurements of the cardiac chambers dimensions including inter ventricular septum diastole (IVSD), LV internal wall diastole, LV posterior wall diastole, and LV systole diameters, as well as aortic (aortic diameters [AoD]), left atrial diameter (LAD) and, left atrial/AoD (LA/AoD), LVFS values, and ejection fraction (EF) was conducted according to the recommendations of the American Society of Echocardiography (ASE) for M-mode echocardiography.^[14] Heart disease among β-TM patient was considered if having at least one of the followings: congestive heart failure or impaired LV contractility defined as having an EF <55% and or a shortening fraction (FS) <30%.^[15] For 2D STE, the recommended method of the ASE was applied;^[16] the grayscale images were obtained from the left ventricle using apical four, two-chamber, and parasternal short-axis (papillary muscle level) views at a frame rate of 60-80 frames/s with an image sector angle of 30° - 60° . At least three consecutive cardiac cycles triggered. Global longitudinal peak systolic strain average (GLPS AVG) was measured. Patients had 24 h electrocardiogram (ECG) holter recorded to assess for arrythmias.

Magnetic resonance imaging acquisition and image analysis

Patients underwent MRI examination using a 1.5-T scanner (Philips-Intera, Holland) Achieva MR Unit and a 12-element phased array coil. Patients were evaluated for

liver siderosis using relaxation parameter T2*. Liver iron content (LIC) measurements were done by acquiring eight consequent T2* values and assessing T2* decay. Liver T2* values were converted into LIC values using the calibration curve.^[17] LIC of >7 mg Fe/g dry liver weight indicated the presence of hepatic hemosiderosis.^[18] For the measurement of myocardial T2*, a single short 20 s breath-hold axis mid-ventricular slice was acquired at eight simultaneously acquired echo times (TEs 1.4–13.6 ms/echo spacing 1.6 ms). The myocardial T2* was calculated using the same method as that in the liver. Cardiac MRI T2* values did not correlate to the age with a mean ranging from 26 to 36.4 ms.^[19-21] Normal level more than 20 ms indicates no iron overload, level <20 ms indicates infiltration of cardiac muscles by iron.^[22]

Statistical analysis

Statistical Program for Social Science version 15 (SPSS Inc., Chicago, IL, USA) was used. Quantitative variables were described in the form of range, mean and standard deviation. Qualitative variables were described as number and percentage. In order to compare parametric quantitative variables between two groups, Student's *t*-test was applied while comparison between three groups was performed using analysis of variance (ANOVA) with post hoc test. Mann-Whitney was used for comparing nonparametric variables between two groups. Qualitative variables were compared using Chi-square (χ^2) test or Fischer's exact test when frequencies were below five. Correlation studies were done using Pearson's correlation coefficient, Spearman correlation test and multiple regression analysis. Receiver operating characteristic (ROC) curve was used to determine the best cutoff value of the studied STE measurements to detect subclinical myocardial iron overload that best combined sensitivity and specificity. The area under the curve (AUC) and 95% confidence interval were calculated for each plot. Patients were then divided into two groups: those with cardiac affection by STE (defined as having a decrease in any of the longitudinal strain parameters to less than the cutoff values found) and those without and were compared as regards all the studied data. A P < 0.05was considered statistically significant in all analyses.

RESULTS

The relevant demographic, clinical, laboratory, and radiological data of all studied β -TM patients are illustrated in Table 1. The median (interquartile range [IQR]) LIC was 13.40 (8.86–25.00) mg Fe/g dry liver weight with 4 (13%) patients with LIC <7 mg Fe/g dry liver weight, while the median (IQR) cardiac T2* was 18.7 (2.1–17.1) ms with 11 (36.6%) patients having a cardiac T2* <20 ms. Longitudinal systolic strain values by STE were significantly lower among the studied patients compared with control values [Table 2]. Figure 1

Table 1: Clinical	, laboratory and	radiol	ogical data
of the studied be	eta-thalassemia	major	patients

Parameters	Total (<i>n</i> =30)
Age at evaluation (years), mean±SD	14.77±2.45
Gender, n (%)	
Female	13 (43.3)
Male	17 (56.7)
Disease duration (month), mean±SD	14.03±2.66
Splenectomy, n (%)	23 (76.7)
Hepatitis C virus, n (%)	11 (36.7)
Chelation type, n (%)	
Monotherapy	8 (26.7)
Combined	22 (73.3)
Total bilirubin (mg/dl), mean±SD	0.90±0.40
Indirect billiburin (mg/dl), mean±SD	0.61±0.31
Mean pretransfusion Hb in the last 2 years (g\dl),	7.07±0.67
mean±SD	
Serum ferritin in last 2 years prior to	1817 (1059-4045)
evaluation (ng/mL), median (IQR)	
M mode echocardiographic, mean±SD	
IVSd (cm)	1.10±0.18
LVIDd (cm)	4.52±0.43
LVPWd (cm)	1.02±0.17
EF%	65.7±8.41
FS%	36.63±6.47
AoD (cm)	2.67±0.249
LAD (cm)	3.41±0.44
LA/AoD	1.28±0.19
Cardiac iron overload with T2 [*] (ms), median (IQR)	12.85 (2.1-17.1)
LIC (mg/g liver dry weight), median (IQR)	13.40
	(8.86-25.00)

IVSd: Inter ventricular septum diastole diameter, LVIDd: Left ventricular internal wall diastole diameter, LVPWd: Left ventricular posterior wall diastole, LAD: Left atrial diameter, AoD: Aortic diameter, FS: Fractional shortening, EF: Ejection fraction, LIC: Liver iron concentration, SD: Standard deviation, IQR: Interquartile range, Hb: Hemoglobin

illustrates the difference in GLS between thalassemia and healthy subjects. All patients had normal 24 h ECG Holter monitoring.

Echocardiographic data (M mode and speckle-tracking) in relation to clinical, laboratory, and demographic data

No significant differences were found between splenectomized and nonsplenectomized, male and female patients as regards echocardiographic data (M mode, speckle-tracking) (P=0.72). Patients on combined chelation had significantly thicker IVSD diameter by M-mode echocardiography compared to those on mono therapy (t = -3.91, P = 0.001); yet patients on mono and those on combined chelation therapy had comparable longitudinal systolic strain values (t = -0.512, P = 0.61). Furthermore, compliance did not have a statistically significant effect on echocardiographic parameters (M mode, speckle-tracking) (t = -1.13, P = 0.26).

Patients with a history of hepatitis C positive virus infection had a significantly lower GLPS AVG values compared to those without (P = 0.033). GLPS AVG values correlated negatively to the age, disease duration as well as total and indirect bilirubin levels (r = -0.39 and P = 0.03 and r = -0.38



Figure 1: Average peak systolic longitudinal strain values reported in a healthy subject (a) and in a β -thalassemia major patient with cardiac iron overload (b)

and P = 0.036, r = -0.51 and P = 0.004 and r = -0.51 and P = 0.004 respectively). No significant correlation was demonstrated between the GLPS AVG values and LDH nor the mean pretransfusion hemoglobin (r = -0.37 and P = 0.22 and r = -0.30 and P = 0.11, respectively). No significant correlation was found between conventional echocardiographic parameters of LV function (EF, FS%) and GLPS AVG (r = -0.23 and P = 0.21 for EF) and (r = -0.22 and P = 0.22 for FS%) but a significant negative correlation between LA/AO diameter and GLPS AVG values was detected (r = -0.45 and P = 0.013) [Figure 2].

Impact of iron overload on echocardiographic data (M mode and speckle-tracking)

We could not demonstrate significant differences between patients with mean serum ferritin <2500 ng/ml and those with mean serum ferritin more than or equal 2500 ng/ml in the last 2 years prior evaluation as regards M mode echocardiographic parameters (P > 0.05). Although, patients with mean serum ferritin >2500 ng/mL in the past 2 years prior evaluation had lower GLPS AVG values than those below this cutoff; yet the differences did not reach statistical significance (Z = -1.646, P = 0.1). Nevertheless, a significant negative correlation was observed between mean serum ferritin in the past 2 years and GLPS AVG (r = -0.42 and P = 0.02) [Figure 3] and a multivariate regression analysis revealed that mean serum ferritin was independently related to longitudinal peak systolic strain cutoff values (GLPS AVG) among thalassemia patients (P = 0.000).

Hepatic iron overload by LIC did not correlate significantly to GLPS AVG (r = -0.08 and P = 0.7). Although we could not find a significant correlation between cardiac MRI T2* values and GLPS AVG (r = 0.19 and P = 0.4), yet patients with cardiac iron overload by MRI T2* had significantly lower GLPS AVG values and increased AoD than those without (P < 0.001 and P = 0.049, respectively) [Table 3].

The ROC curve analysis revealed that longitudinal peak systolic strain cutoff values of \leq -19 was able to detect β -TM patients having subclinical cardiac iron overload by MRI T2* with a balanced sensitivity of



Figure 2: Correlation between LA/AoD and GLPS AVG. LA: Left atrial, AoD: Aortic diameters, GLPS AVG: Global longitudinal peak systolic strain average

Table 2: Comparison between beta-thalassemia patients and controls as regards demographics, M-mode and 2D speckle echocardiographic data parameters

	Me	Test	Р	
	Control group (<i>n</i> =30)	Patients group (<i>n</i> =30)		
Gender, n (%)	17 (56.7) 13 (43.3)	17 (56.7) 13 (43.3)	0.000*	1.000
Age (years)	15.33 ± 2.32 -22 (-2320)	14.77±2.45	0.909 ^{\$} 3.326#	0.367
median (IQR)	-22 (-20 -20)	-10.2 (-20.1 - 10.0)	0.020	0.001
IVSD (cm) LVIDd (cm)	0.74±0.06 4.85±0.41	1.10±0.18 4.52±0.43	10.392 ^{\$} 3.042 ^{\$}	<0.001 0.004
LVPWd (cm)	0.82±0.08	1.02±0.17	5.830 ^{\$} 0.938 ^{\$}	<0.001
FS%	38.60±3.69	36.63±6.47	1.449 ^s	0.153
AoD (cm) LAD (cm) LA/AoD	2.82±0.22 2.89±0.38 1.01±0.12	2.67±0.24 3.41±0.44 1.28±0.19	2.523 ^{\$} 4.899 ^{\$} 6.581 ^{\$}	0.014 <0.001 <0.001

^{*}Chi-square test, ^{\$}Independent *t*-test, [#]Mann-Whitney test. GLPS AVG: Global longitudinal peak systolic strain average, IVSd: Inter ventricular septum diastole diameter, LVIDd: Left ventricular internal wall diastole diameter, LVPWd: Left ventricular posterior wall diastole, LAD: Left atrial diameter, AoD: Aortic diameter, FS: Fractional shortening, EF: Ejection fraction, SD: Standard deviation, IQR: Interquartile range

90% and specificity of 100% and a positive predictive and a negative predictive values of 100% and 90.9% respectively (AUC, 0.96) [Figure 4]. Table 4 gives a breakdown of the previously published studies assessing the longitudinal peak systolic strain cutoff values in β -thalassemia patients in relation to the cardiac iron overload by cardiac MRI T2*.

Comparison between beta thalassemia major patients with cardiac affection by speckle-tracking echocardiography (longitudinal peak systolic strain \leq -19) and those without

Eight of our β -TM patients had decreased longitudinal strain values \leq -19; patients with decreased longitudinal

Table 3: Comparison between beta-thalassemia patients with cardiac iron overload by magnetic
resonance imaging T2* and those without as regards speckled and M-mode echocardiographic data

	Mean	Test value	Р		
	No cardiac iron overload (<i>n</i> =19)	Cardiac iron overload (n=11)			
GLPS AVG, median (IQR)	-22 (-2320)	-19.5 (-20.518.5)	24.242#	<0.001	
IVSd (cm)	1.11±0.17	1.03±0.18	59.350 ^{\$}	0.097	
LVIDd (cm)	4.40±0.31	4.68±0.60	4.619 ^{\$}	0.585	
LVPWd (cm)	1.08±0.18	0.98±0.17	17.271 ^{\$}	0.182	
EF (%)	67.73±8.46	62.38±10.00	1.065 ^{\$}	0.072	
FS (%)	38.27±6.89	34.13±7.22	1.603 ^s	0.203	
AoD (cm)	2.62±0.18	2.83±0.24	5.307 ^{\$}	0.049	
LAD (cm)	3.28±0.34	3.63±0.39	12.364 ^{\$}	0.420	
LA/AoD	1.25±0.14	1.28±0.18	21.178 ^{\$}	0.577	

IVSd: Inter ventricular septum diastole diameter, LVIDd: Left ventricular internal wall diastole diameter, LVPWd: Left ventricular posterior wall diastole, LAD: Left atrial diameter, AoD: Aortic diameter, FS: Fractional shortening, EF: Ejection fraction, SD: Standard deviation, IQR: Interquartile range, GLPS AVG: Global longitudinal peak systolic strain average, #: Mann-Whitney test, \$: Independent t-test

strain had significantly higher mean serum ferritin in the last 2 years, higher total bilirubin levels (t = -1.99and P = 0.047 and t = -3.44 and P = 0.002, respectively). Both groups had comparable age at diagnosis (t = 0.35and P = 0.72), disease duration (t = -1.366 and P = 0.18), frequency of HCV infection (t = 1.53 and P = 0.22), mean pretransfusion Hb in the last 2 years (t = 1.73 and P = 0.09), serum LDH levels (t = -1.94 and P = 0.052), and LIC values (t = -0.73 and P = 0.46).

DISCUSSION

Speckle tracking-derived strain can give a measure of both global and regional cardiac function.^[23] Global longitudinal strain (GLS) allows the clinicians to detect early cardiac dysfunction in β -thalassemia anemia.^[24,25] Our goal was to evaluate the clinical utility of STE as a tool for early detection of myocardial disease in transfusion dependent β -TM patients.

Our β -TM patients had no clinical heart disease with a mean EF% and FS% of 65.7 ± 8.41 and 36.63 ± 6.47, respectively, yet the longitudinal systolic strain values by STE were significantly lower compared to standard control values which might reflect an early LV dysfunction. Observations similar to our study were illustrated by Parsaee *et al.*^[3] who evaluated early cardiac dysfunction using STE in children with transfusion-dependent β -TM on iron chelation therapy and found a significant reduction in GLS compared to normal subjects' group. In contrast, Monte *et al.*^[26] reported no significant differences in the longitudinal strain values between thalassemia and healthy controls.

In our study, we could not find a significant correlation between conventional echocardiographic parameters of LV function (EF, FS%) and GLPS AVG which was in concordance with Abtahi *et al.*^[27] who failed to find a significant association between EF and MRI T2* findings, indicating their inefficiency in predicting abnormal deposition of cardiac iron as well as early diagnosis of heart failure in patients with thalassemia. LA/Ao and



Figure 3: Correlation between mean serum ferritin in the last 2 years and GLPS AVG. GLPS AVG: Global longitudinal peak systolic strain average

LA diameter were higher among our β -TM patients with cardiac iron overload by cardiac MRI T2* than those without, yet results did not reach statistical significance. Nevertheless, we demonstrated a significant negative correlation between LA/AO diam and all longitudinal strain parameters and a significantly increased AoD by M mode echocardiography in patients with decreased longitudinal strain than those without. However, Leonardi *et al.*^[28] reported a poor correlation between echocardiographic diastolic function parameters and myocardial T2* in β -TM patients.

When evaluating the relation of longitudinal strain and the clinical as well as the laboratory parameters, we found that GLPS AVG values correlated negatively to the age as well as the disease duration but not to the mean pretransfusion hemoglobin. Narayana *et al.*^[6] found that the age of the children with β -thalassemia and their hemoglobin percentages correlated well with the cardiac parameters such as LVEF, mitral E/A ratio, and GLS.

Investigating the association of longitudinal strain data with hemolytic markers, we found that GLPS AVG

Table 4: Illustration of the published studies assessing the longitudinal peak systolic strain cutoff values in beta-thalassemia patients in relation to the cardiac iron overload by cardiac magnetic resonance imaging T2*

Study	Number of βTM patients	Age (years), mean±SD	GLS average in β TM with CMRI (T2 [•] \leq 20 ms)	GLS average in βTM with CMRI (T2 [:] >20 ms)	GLS average cut-off values	Sensitivity (%)	Specificity (%)	Limitations
Garceau <i>et al.</i> , 2011 ^[39]	40	34.4±11	-16±3	-20±2	≤-17	76	88	Selection bias Variability between observers not assessed
Ari <i>et al</i> ., 2017 ^{*[40]}	30	14.6±3.6	-19.7±3.1	-23.1±2.2	-	-	-	Small sample size Intra-and inter-observer variability not assessed
Poorzand et al., 2017	44	23.51±6.2	-18.23±3.41	-20.28±1.67	≤-17.5	43.8	100	1 week gap between the CMRI and echo studies Selection bias
Parsae <i>et al.</i> , 2018	122	30.79±9.37	–17.00 (IQR–19-–16)	-19.00 (IQR-20- -18)	≤-18.5	73	63	-
Pizzino <i>et al.</i> , 2018 ^{*[41]}	28	37.4±10	-18.3±2	-21.3±2.7	-	-		Small sample size
Abtahi et al., 2019	50	23.7±5	-17.64±2.56	-21.55±2.68	≤-19.5	82.14	86.36	No control group
Current study	30	14.77±2.45	–19.5 (IQR–20.5-–18.5)	-22 (IQR-2320)	≤-19	90	100	Small sample size Intra-and inter-observer variability not assessed

No cutoff values assessed. GLS average: Average global longitudinal systolic strain, βTM: Beta-thalassemia major, CMRI: Cardiac magnetic resonance imaging, SD: Standard deviation, IQR: Interquartile range



Figure 4: ROC curve analysis to detect the longitudinal peak systolic strain cutoff values in relation to subclinical cardiac iron overload by MRI T2*. GLPS AVG: Global longitudinal peak systolic strain average, ROC: Receiver–operating characteristic, MRI: Magnetic resonance imaging, GLPS LAX: Global longitudinal peak systolic strain longitudinal axis, GLPS A4C: Global longitudinal peak systolic strain four chambers apical, GLPS A2C: Global longitudinal peak systolic strain two chambers apical

correlated negatively to the total and indirect bilirubin levels but there was no significant correlation between longitudinal strain values and LDH; in addition, we found a significantly higher total bilirubin levels in patients with decreased longitudinal strain than those without, but LDH was comparable between both groups. Whipple *et al.*^[29] found no association between right ventricular GLS (RVGLS) and LV GLS (LVGLS) and LDH or indirect bilirubin levels in children with sickle cell disease (SCD), but Barbosa *et al.*^[30] found that lactate dehydrogenase as an assessment of intensity of hemolysis was independently associated with abnormal LVGLS in adults with SCD. The association of increased bilirubin with GLS affection is probably a reflection of the underlying contribution of hemolysis to the hyperdynamic cardiac state in β -thalassemia.

Although serum ferritin is an acute phase protein, and hence, its levels can be influenced by inflammation, infection, and liver damage which could limit its clinical value to determine cardiac iron overload as confirmed by the published studies^[31] but it has been used for decades as a predictor of iron overload status in the clinical practice due to its strong correlation with hepatic iron as well as being inexpensive and accessible. In our study, we have found that mean serum ferritin in the last 2 years correlated negatively to longitudinal systolic strain values (GLPS AVG) and those patients with mean serum ferritin >2500 ng/mL in the past 2 years prior evaluation had lower GLPS AVG values than those below this cutoff; yet the differences did not reach statistical significance. This comes in concordance with Chen et al.[32] who showed an abnormal GLS despite preserved global LV systolic function among thalassemic patients with serum ferritin levels >2000 ng/ml.

Hepatic MRI method proved to be the gold standard for evaluation and monitoring liver iron concentration (LIC) which is considered the best measure of total iron loading.^[33] We could not demonstrate a significant correlation between LIC and speckle tracking nor M mode echocardiographic data. In a study by Farhangi *et al.*^[34] assessing cardiac and liver iron load in thalassemia major patients, they did not show any significant differences between mean of liver T2* (ms) and echocardiography results (EF and FS%).

There is no consensus about a well-defined cut-off value of regional LS and GLS to distinguish pathological and physiological hypertrophy in the literature particularly in thalassemia.^[35] Using ROC curve, we found that GLPS cutoff value of \leq -19 was able to detect β -TM patients having subclinical cardiac iron overload by MRI T2* with a sensitivity of 90% and a specificity of 100%. Poorzand *et al.*'s^[24] study yielded a significant relation between longitudinal strain and myocardial T2* among β -TM patients, yet they found a cutoff point of -17.5 with a specificity of 100% and a sensitivity of 43.8%. Furthermore, Parsaee *et al.*^[36] argued that the optimal cutoff value for GLS was -18.5 among their β -TM patients with sensitivity and specificity 73.0% and 63.0%, respectively. Abtahi *et al.*^[27] found an even higher cut off value for GLS (<-19.5).

We used the cutoff values of ≤ -19 for GLPS to divide our β -TM patients into 2 groups those with cardiac affection by STE (GLPS ≤ -19) and those without (GLPS ≥ -19) and found that patients with decreased longitudinal strain had significantly higher mean serum ferritin in the last 2 years, yet LIC values were comparable in both groups.

In our study, there were no significant correlations between cardiac MRI T2* and speckle echocardiographic

parameters but there were significantly lower GLPS AVG values in patients with cardiac iron overload by MRI T2* (<20 ms); moreover, cardiac MRI T2* values were lower in those with cardiac affection by STE compared to those without, yet results did not reach statistical significance. This comes in agreement with Parsaee et al.[3] who found no significant correlation between GLS and cardiac MRI T2* values of β-TM patients. In contrast, Pizzino et al.[37] showed a significant correlation between GLS and T2* values and that β-TM Patients with impaired GLS had a significant higher risk of myocardial iron overload detected by cardiac MRI T2*. Longitudinal strain (LS) appears to be affected by both clinical and technical issues and among the clinical issues, age play the greatest roles and it recently was demonstrated that LS decreases with age.[35,38] Therefore, we attributed the lack of such correlation to the young age of our study population as well as the small sample size and hence the limited number of thalassemia patients with cardiac affection at this young age group.

Limitations

The presence of a relatively small sample size is one limitation which might have an impact on the validation of the efficiency of this method. Since many variables were addressed, a larger sample would have been more convenient. Another limitation of the study is the absence of statistical analysis of the inter- and intra-observer variability to evaluate the reproducibility of STE. Published data suggested that three-dimensional (3D) STE is more capable of assessment of the actual global myocardial deformation compared to 2D speckle imaging. A follow-up study is warranted to determine whether 3D STE may be more sensitive than 2D STE in the detection of early myocardial affection in β T-M patients.

CONCLUSION

Our results illustrated an abnormal GLS despite preserved LV systolic functions among β T-M patients. These myocardial functional changes appear to be related to the disease duration, high ferritin, degree of hemolysis as well as to Ao diameter. Thus, 2D STE might be used as an alternative method to detect early cardiac affection in β T-M before evident systolic dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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