Global longitudinal strain by cardiac magnetic resonance is associated with cardiac iron and complications in beta-thalassemia major patients

ABSTRACT

Background: The aim of this cross-sectional study was to investigate the association of left ventricular (LV) strain parameters with demographics, clinical data, cardiovascular magnetic resonance (CMR) findings, and cardiac complications (heart failure and arrhythmias) in patients with β-thalassemia major (β-TM).

Method: We considered 266 β-TM patients (134 females, 37.08±11.60 years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) project and 80 healthy controls (50 females, mean age 39.77±11.29 years). The CMR protocol included cine images for the assessment of global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) using feature tracking (FT) and for the quantification of LV function parameters, the T2* technique for the assessment of myocardial iron overload, and late gadolinium enhancement (LGE) technique.

Results: In comparison to the healthy control group, β-TM patients showed impaired GLS, GCS, and GRS values.

Among β-TM patients, sex was identified as the sole independent determinant of all LV strain parameters. All LV strain parameters displayed a significant correlation with LV end-diastolic volume index, end-systolic volume index, mass index, and ejection fraction, and with the number of segments exhibiting LGE. Only GLS exhibited a significant correlation with global heart T2* values and the number of segments with T2*<20 ms. Patients with cardiac complications exhibited significantly impaired GLS compared to those without cardiac complications.

Conclusion: In patients with β-TM, GLS, GCS, and GRS were impaired in comparison with control subjects. Among LV strain parameters, only GLS demonstrated a significant association with cardiac iron levels and complications.

INTRODUCTION

Beta-thalassemia is the most common form of hemoglobinopathy, determined by a shortfall in the production of β chains of hemoglobin [1]. Individuals with β-thalassemia major (TM), representing the most severe form of the disease, require lifelong, regular transfusions to sustain their life. Since humans have no physiologic mechanism for active elimination of excess iron, regular transfusions cause progressive iron accumulation in vital organs [2]. The excessive iron buildup in the heart is responsible for cardiac dysfunction and ultimately leads to heart failure, which represents the primary cause of morbidity and mortality among β-TM patients [3, 4]. Iron overload-induced cardiomyopathy might potentially be reversed with the initiation of early and intensive chelation therapy [5, 6]. Therefore, timely detection of myocardial iron overload (MIO) is crucial to prevent the progression of heart failure. In recent years, patient survival rates have significantly improved, largely due to the non-invasive assessment of MIO using T2* cardiovascular magnetic resonance (CMR) [4, 7]. This method enables personalized chelation therapies tailored to each patient's requirements and facilitates the evaluation of treatment effectiveness [8, 9]. It has been demonstrated that as the severity of MIO, measured by T2* values, increases, there is a progressive decrease in left ventricular ejection fraction (LVEF) [10]. However, early MIO is not detected by changes in LVEF [11, 12]. Myocardial strain analysis using CMR-feature tracking (FT) can assess subclinical myocardial contractility function before LVEF impairment occurs [13]. In particular, myocardial strain enables a more comprehensive assessment of contractile function by evaluating the deformation of all three layers of myocardial fibers: subendocardial, subepicardial, and transmural fibers. The subendocardial fibers, represented by the global longitudinal strain (GLS), contribute to longitudinal shortening. The subepicardial fibers, represented by the global circumferential strain (GCS), contribute to circumferential shortening [13]. Finally, the transmural fibers, represented by the global radial strain (GRS), contribute to myocardial radial thickening [14, 15]. Identification of pre-clinical imaging biomarkers of cardiac dysfunction in β-TM patients is undoubtedly valuable in clinical practice.

The aim of this study was to evaluate the cross-sectional relationship of the CMR-derived LV strain values with demographics, clinical data, CMR parameters, and cardiac complications among β-TM patients.

METHODS

Study population

We considered 266 β-TM patients (134 females, 37.08±11.60 years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) project, a network consisting of 66 thalassemia centers and 15 magnetic resonance imaging (MRI) sites in Italy. Within this network, CMR examinations are conducted using standardized and validated protocols [16]. The centers are interconnected through a web-based database which serves as a centralized system for collecting various types of information, including demographic details, clinical records, laboratory results, and CMR findings.

All patients received scheduled blood transfusions every 2 to 5 weeks since early childhood to sustain a targeted pre-transfusion hemoglobin concentration ranging from 9 to 10 g/dL. CMR scanning was performed within one week before the scheduled blood transfusion. All patients started undergoing chelation therapy from the mid-to-late 1970s, and those individuals born after this period commenced chelation treatment during their early childhood years.

The study also included 80 healthy subjects (50 females, mean age 39.77±11.29 years) considered as the control group. Inclusion criteria were: normal electrocardiogram, no history of cardiac diseases or symptoms, no cardiovascular risk factors, no known systemic diseases, and no absolute contraindications to the CMR.

All subjects gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

CMR

CMR exams were performed in the reference MR center (Pisa) of the E-MIOT Network using a 1.5T scanner (Signa Excite HD or Signa Artist, GE Healthcare, Milwaukee, WI, USA). A cardiac phased-array receiver surface coil (30-elements) with breath-holding and ECG gating was used.

Steady-state free precession (SSFP) cines were acquired during 8-second breath holds in the vertical and horizontal long axis (LAX) planes, with subsequent contiguous 8-mm short-axis (SAX) slices from the atrio-ventricular ring to the apex [17]. The most apical slice included was the first slice displaying no blood pool at end-diastole. The most basal slice included was the one that showed a remaining part of the thick myocardium and was below the aortic valve. Thirty cardiac phases were acquired per heartbeat. Offline post-processing was performed using a commercially available software system (Circle CVI42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Feature-tracking analysis was performed by a single operator (R.C.). The endocardial and epicardial borders of the LV were hand-drawn on the end-diastolic and end-systolic frames excluding trabeculae, papillary muscles, pericardium, and epicardial fat. For each subject, the end-diastolic and end-systolic phases had to be identical in all SAX and LAX slices. The contours were then automatically propagated (tracked) through the cardiac cycle by matching individual patterns representing anatomical structures. The quality of the tracking was checked visually and, if the automatic boundary tracking was not accurate, the contours were manually adjusted, and the algorithm was reapplied. Then, three-directional LV strains were derived: global circumferential strain (GCS), which is the expression of cardiomyocytes shortening along the LV circular perimeter, global radial strain (GRS), representing the myocardial deformation toward the center of the ventricular cavity and depicted by a positive value, and global longitudinal strain (GLS), representing the longitudinal shortening of the cardiac muscle, from the base to the apex of the heart. Circumferential and radial strains were derived from the SAX stack, while GLS was assessed in the three LAX views.

The quantification of LV function parameters from SSFP cine images was based on the manual recognition of the endocardial and epicardial LV contours in end-diastolic and end-systolic phases in each slice. The papillary muscles were outlined and regarded as part of the myocardial mass. End diastolic volume (EDV) and end-systolic volume (ESV) were identified, respectively, by the global maximum and minimum LV cavity volume. The LV mass was calculated by multiplying the volume of the myocardium by its specific weight (1.05 g/cm3). The ejection fraction (EF) was given by the ratio between the stroke volume (difference between EDV and ESV) and the EDV. LV volumes and mass were indexed to the body surface area (BSA).

Segmental wall motion was visually assessed in cine images.

Myocardial iron overload (MIO) was assessed by acquiring three parallel SAX views (basal, medium, and apical) of the LV with a T2* gradient–echo multiecho sequence [18]. Image analysis was performed using a custom-written, previously validated software (HIPPO MIOT®) [19], which enabled the T2* assessment in all the 16 LV segments, according to the standard AHA/ACC model [20]. Susceptibility artefacts were compensated by applying an appropriate correction map [19]. The global heart T2* value was calculated as the mean of all segmental values.

To detect replacement/focal myocardial fibrosis, late gadolinium enhancement (LGE) images were acquired in the same planes of the cine SSFP images by a T1-weighted gradient-echo inversion-recovery pulse sequence, 8–18 min after the intravenous administration of Gadobutrol (Gadovist®; Bayer Schering Pharma; Berlin, Germany) at the standard dose of 0.2 mmol/kg of body weight. LGE image acquisition was not done in patients with a glomerular filtration rate <30 mL/min/1.73m2 and in patients who refused the contrast medium administration. LGE was evaluated visually using a two-point scale (absent or present), and enhancement was considered present whenever it was visualised in two different views [21]. The extent of LGE was quantified in the number of segments involved using the standard AHA/ACC model.

Diagnostic criteria

A T2* measurement of 20 ms was taken as a "conservative" normal value for the segmental and global heart T2* values [10, 19]. A global heart T2*<20 ms indicated significant MIO.

Diabetes mellitus was defined as fasting plasma glucose ≥ 126mg/dl or 2-h plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT) or random plasma glucose ≥ 200 mg/dl with classic symptoms of hyperglycaemia or hyperglycaemic crisis [22].

Cardiac complications were defined as a composite of either heart failure (HF) or arrhythmias, clinically active at the time of the CMR. The diagnosis of HF was made by clinicians based on clinical symptoms, signs, and instrumental findings, according to the current guidelines [23]. Arrhythmias were diagnosed through a combination of medical history, physical examination, and standard electrocardiogram (ECG) or 24-h ECG Holter monitoring and were classified according to the AHA/ACC guidelines [24].

Statistical Analysis

All data were analysed using SPSS version 27.0 (IBM Corp, Armonk, NY) and MedCalc version 19.8 (MedCalc Software Ltd, Ostend, Belgium) statistical packages.

Continuous variables were described as mean±standard deviation (SD) and categorical variables were expressed as frequencies and percentages.

The normality of the distribution of the parameters was assessed by using the Kolmogorov-Smirnov test.

The comparison between two groups was done using the independent-samples t-test for continuous values with normal distribution, the Wilcoxon rank sum test for continuous values with non-normal distribution, and the $\chi 2$ testing for categorical data.

Correlation analysis was performed using Pearson's or Spearman's tests where appropriate.

The stepwise multivariate regression analysis was carried out to identify the determinants of LV strain parameters. The collinearity of variables tested in the multivariate model was assessed using the variance inflation factor (inflated if >5) and its tolerance statistic (inflated if <0.20).

The receiver operating characteristic (ROC) analysis was applied to estimate the diagnostic value of LV strain parameters for detecting a specific condition. The results were presented as areas under the curve (AUCs) with 95% confidence intervals (CIs) and the optimal cut-off value was calculated using the Youden index method.

A 2-tailed probability value of 0.05 was considered statistically significant in all tests.

RESULTS

Comparison between healthy subjects and β-TM patients

Table 1 shows the demographic and clinical characteristics of TM patients.

No significant difference between healthy subjects and TM patients was found in terms of age ($p=0.228$) and sex ($p=0.953$).

Compared to healthy subjects, TM patients showed significantly increased LV EDV index (85.97±17.23 ml/m2 vs. 75.93±12.42 ml/m2 $p<0.0001$), LV ESVI index (32.46±11.03 ml/m2 vs. 27.85±7.31 ml/m2 $p=0.002$), and LV mass index (61.39±12.92 g/m2 vs. 55.45±12.64 g/m2 $p<0.0001$) but a comparable LV EF (62.35±7.07 % vs. 63.52±6.29 % $p=0.349$).

All three LV strain parameters were significantly impaired in TM patients than in healthy subjects (GCS: -14.74±2.73 % vs. -16.69±2.09 % $p<0.0001$; GRS: 22.73±5.76 % vs. 26.34±5.08 % $p<0.0001$; GLS: -14.52±2.26% vs. -17.91±1.91 % $p<0.0001$) (Figure 1).

In healthy subjects, all LV strain values were independent of age but were influenced by sex, with females exhibiting a greater deformation than males (GCS: mean difference=1.36 % $p=0.003$; GRS: mean difference=3.29 % $p=0.003$; GLS: mean difference=1.53 % $p<0.0001$).

Demographic and clinical correlates of LV strains in TM

Table 2 shows the correlation of LV strains with demographic and clinical characteristics of TM patients.

There was a significant sex difference in all global strain values, with a greater deformation among females (GCS: -15.32±2.59 % vs. -14.16±2.74 % vs. p<0.0001; GRS: 23.99±5.82 % vs. 21.44±5.43 % p<0.0001; GLS: -15.08±2.42 % vs. -13.96±1.93 % p<0.0001). All strains were independent from age, age at start of regular transfusion and chelation, presence of diabetes, and levels of pre-transfusion hemoglobin and ferritin (p>0.05). LV GRS was significantly reduced in splenectomised patients compared to non-splenectomised patients (21.99±6.022 % vs. 23.49±5.39 % p=0.012). All LV strain parameters significantly correlated with body surface area (GCS: R=0.201 p=0.001; GRS: R=-0.202 p=0.001; GLS: R=0.118 p=0.050).

For each type of strain (dependent variable), a multivariable analysis was conducted, including as independent variables all demographic/clinical parameters found to be statistically significant at the univariate analysis (Table 3). Sex emerged as the only significant predictor of all strain measures (GCS: standardized β coefficient=-0.214 p<0.0001; GRS: standardized β coefficient=0.222 p<0.0001; GLS: standardized β coefficient=-0.247 p<0.0001). No variable was excluded from the multivariable models due to excessive collinearity.

All LV strains were significantly correlated with each other (GCS and GRS: R=-0.950 p<0.0001; GCS and GLS: R=0.446 p<0.0001; GRS and GLS: R=-0.473 p<0.0001).

Association between LV strains and myocardial iron overload

The LV GCS and GRS were not correlated to cardiac iron levels, while the GLS exhibited a significant association with global heart T2* values (R=-0.158 p=0.010) and with the number of segments with T2*<20 ms (R=0.185 p=0.002) (Table 2).

The LV GLS was significantly lower in patients with significant MIO than in patients without MIO (-13.59±2.35 % vs. -14.65±2.22 % p=0.017) (Figure 2A).

Analysis of the ROC curve (Figure 2B) showed an area under the curve of 0.63 (95%CI=0.57-0.69) with a best GLS cut-off of -12.76% for the detection of significant MIO (p=0.019). This cut-off had a sensitivity of 43.8% (95%CI=26.4-62.3%) and a specificity of 84.6% (95%CI=79.3-89.0%).

Correlation between strains and other measures of systolic function and LGE

Table 2 shows the CMR characteristics of TM patients and their association with LV strains.

All LV strains were significantly correlated with LV end-diastolic volume index (GCS: R=0.442 p=<0.0001; GRS: R=-0.429 p<0.0001; GLS: R=0.161 p=0.008), LV end-systolic volume index (GCS: R=0.584 p<0.0001; GRS: R=-0.578 p<0.0001; GLS: R=0.308 p<0.0001), LV mass index (GCS: R=0.352 p<0.0001; GRS: R=-0.340 p<0.0001; GLS: R=0.228 p<0.0001), and LV EF (GCS: R=-0.513 p<0.0001; GRS: R=0.521 p<0.0001; GLS: R=-0.313 p<0.0001).

Abnormal LV motion was found in 26 (9.8%) patients: 23 hypokinetic and 3 dyskinetic. Compared with patients without LV motion abnormalities, patients with abnormal LV motion showed significantly lower LV GCS (-12.59±2.21 % vs. -14.98±2.68 % p<0.0001), GRS (17.88±4.26 % vs. 23.25±5.66 % p<0.0001), and GLS (-12.39±2.92 % vs. -14.75±2.05 % p<0.0001).

One-hundred and seventy-three (65.0%) patients received the contrast medium and LV LGE was detected in 70 (40.5%) of them. The majority of the patients (N=68) had a non-ischemic LGE pattern, while two patients had a transmural LGE pattern. The 74.3% of patients had at least two or more foci of fibrosis, with the septum involved in the 81.4% of the cases. LV GCS and GLS were comparable between patients without and with LGE, while LGE was associated with significantly reduced LV GRS (21.06±5.55 % vs. 22.71±5.16 % p=0.039). In the subgroup of LGE-positive patients, the number of segments with LGE (mean: 2.74±1.94; range: 1-9) significantly correlated with all LV strains (GCS: R=0.411, p<0.0001; GRS: R=-0.415, p<0.0001; GLS: R=0.377, p<0.0001).

Link between LV strains and cardiac complications

Twenty-two (8.3%) patients had at least one cardiac complication: nine patients had HF and 13 arrhythmias. Supraventricular arrhythmias (atrial fibrillation and atrial flutter) were the most common type of arrhythmia (10/13=76.9%).

No significant difference between patients without and with cardiac complications was found in global heart T2* values (35.89±11.07 ms vs. 34.09±11.32 ms; p=0.222), LV GCS (-14.82±2.65 % vs. -13.89±3.39 %; p=0.213), LV GRS (22.87±5.48 % vs. 21.19±8.27 %; p=0.079), and LV EF (62.67±6.61 % vs. 58.77±10.51 %; p=0.191). Compared to patients free of cardiac complications, patients with cardiac complications exhibited a significantly reduced LV GLS (-12.64±3.39 % vs. 14.69±2.05; p=0.006) (Figure 3A).

Analysis of the ROC curve (Figure 3B) showed an area under the curve of 0.68 (95%CI=0.62-0.73) with a best GLS cut-off of -11.85 % for the detection of cardiac complications (p=0.012). This cut-off had a sensitivity of 50.0% (95%CI=28.2-71.8%) and a specificity of 91.8% (95%CI=87.6-94.9%). The ROC curve did not reveal a global heart T2* threshold [AUC=0.58 (95%CI=0.51-0.64); p=0.187] or a LV EF threshold [AUC=0.58 (95%CI=0.52-0.64); p=0.258] below which the probability of detecting the presence of cardiac complications increases significantly with satisfying sensitivity and specificity.

DISCUSSION

This study emphasized important findings regarding the LV strain parameters in β-TM patients: (1) β-TM patients demonstrated an impairment of all three myocardial layers represented by GLS, GCS, and GRS values in comparison with healthy subjects; (2) in β-TM patients, sex emerged as the only independent determinant of all left ventricular strain parameters; (3) the number of segments with LGE significantly correlated with all LV strain parameters; (4) among LV strain parameters, only

GLS showed a significant relationship with cardiac iron levels; (5) GLS was more reduced in patients with cardiac complications compared to patients free of complications.

Considering the known association between LV strain and adverse outcomes in various cardiovascular diseases [25, 26], the identification of ventricular strain impairment in β-TM may help to risk stratify patients.

Patients with β-TM demonstrated an impaired GLS, GCS, and GRS compared to the control group. This finding aligns with a recent systematic review which highlighted that most published studies demonstrated statistically significant differences in left LV strain parameters measured by speckle tracking echocardiography between β-TM patients and healthy subjects [27]. The impairment of all three myocardial layers may be linked to the multifaceted nature of β-TM-related cardiomyopathy. This condition involves an interplay between various factors beyond MIO, including chronic anemia, characterized by volume overload from hyperkinetic circulation with increased preload, and a decrease in systemic vascular resistance due to increased arterial stiffness, leading to decreased afterload [28, 29]. The consequence of this chronic hemodynamic state is myocardial wall stress with an impairment of all subendocardial, subepicardial, and transmural fibers [30, 31]. Other factors that can influence LV strain parameters in β-TM include repeated transfusions, which increase the risk of viral infections, subclinical myocarditis, genetic factors, and chronic immunodeficiency [32, 33]. The absence of a difference in the LV EF between healthy subjects and TM patients confirms that the LV EF is not a reliable index for the early detection of cardiac involvement [34, 35].

The finding regarding the significant association between sex and LV strain parameters aligns with current literature describing sex-based difference in strain parameters [36, 37]. A potential explanation of this association in β-TM patients may be linked to the more anemic state in females compared to males, as described by Marsella et al., resulting in increased myocardial wall stress [38]. In line with previous studies [39-42], we have demonstrated that GLS correlated with cardiac iron levels. The MIO concentration begins with a predominant involvement of the subepicardial layer, and subsequent loss of myocardial fibers gradients in the advanced stage [43, 44]. In the presence of iron

overload, ferrous iron enters myocytes through voltage-dependent L-type calcium channels. Within myocytes, iron is stored as ferritin, hemosiderin, and labile cellular iron. Labile iron promotes the formation of reactive oxygen species via the Fenton reaction, converting ferrous to ferric iron and generating toxic radicals. Concurrently, increased transport of ferrous iron through L-type calcium channels disrupts cardiomyocyte calcium transport and impairs excitation-contraction coupling [43]. The association of longitudinal function with MIO may be related to the vulnerability of the subendocardial layers (represented by GLS) to ischemic, toxic, and metabolic factors [40].

The present study demonstrated a correlation between the number of segments exhibiting LGE, indicative of replacement fibrosis, and LV strain mechanism. The association between LGE and LV strain was explored in different cardiovascular diseases, demonstrating that the LV LGE resulted in altered LV deformation values [45-47]. In particular, our findings reveal that the extent of LGE is the primary determinant of LV strain impairment in β-TM patients. Romano et al, in their multicenter CMR-FT study of 1012 patients with ischemic and non-ischemic dilated cardiomyopathy, reported that higher extents of LGE were found in subgroups with more depressed LV strain parameters [48]. This suggests that the number of segments involved by LV LGE may influence the contractility of all myocardial fibers, leading to LV deformation dysfunction [48]. Considering the connection between LGE and adverse outcomes in β-TM patients [49, 50], identifying factors associated with myocardial fibrosis could aid in risk stratification for these patients.

Finally, our study has established an association between impaired GLS and a history of cardiac complications. A GLS < -11.85 % could predict cardiac complications with satisfying sensitivity and specificity. Conversely, global myocardial T2* was comparable between patients with and without cardiac complications. It is likely that in our population of well-treated patients, who are generally not heavily burdened at the cardiac level, GLS emerges as a more sensitive marker of cardiac complications compared to global T2*, even before overt cardiac dysfunction or heart failure develops. due to the lower sample size. Likely due to the lower sample size (N=56), a previous study

failed to detect an association between an history of atrial fibrillation and LV GLS assessed by speckle tracking echocardiography [51].

The relatively low sensitivity of GLS to predict significant MIO and cardiac complications can be due to the low number of positive cases and to the presence of multiple determinants.

Clinical implications

Our data emphasize the importance of evaluating LV strain parameters, particularly GLS, for two main reasons in the routine CMR assessment of β-TM patients. Firstly, GLS can serve as an indirect marker for screening and detecting myocardial iron overload [52], especially in patients who may benefit from abbreviated CMR protocols due to the inability to undergo lengthy CMR examinations due to concomitant cardiac symptoms [53, 54]. Secondly, GLS may serve as an additional non-contrast CMR marker, even in a well-treated population of β-TM patients, for detecting cardiac complications. This underscores the multifaceted nature of iron-overload cardiomyopathy, indicating cardiac damage that extends beyond mere myocardial iron overload.

Limitations

This study has several limitations that should be acknowledged. Firstly, the sample size was relatively small. While our study produced encouraging results, it is imperative to carry out additional research involving a larger patient population to corroborate our findings. Secondly, the study was cross-sectional in design, and we did not assess the predictive value of LV strain parameters for adverse cardiovascular events in β-TM patients, nor did we examine changes in LV function during follow-up. Future longitudinal studies are needed to evaluate the prospective association of these CMR

parameters with patient outcomes and to investigate quantitative changes in LA strain parameters during follow-up CMR scans.

CONCLUSION

In β-TM patients, GLS, GCS, and GRS demonstrated impaired values compared to healthy subjects with similar age and sex distribution. LV strain parameters showed a significant correlation with the number of segments with LV LGE, and GLS displayed a significant correlation with myocardial iron overload. Additionally, GLS strain may serve as an additional non-invasive marker for detecting cardiac complications.

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Table 1. Demographic, clinical, and CMR data of TM patients.

Variable	TM patients (N=266)
Females, N (%)	134 (50.4)
Age (years)	37.08±11.60
Age at start of regular transfusions (months)	17.64±15.93
Chelation starting age (years)	5.04±4.63
Splenectomy, N (%)	136 (51.1)
Body surface area (m2)	1.59±0.23
Pre-transfusion hemoglobin (g/dl)	9.67±0.53
Serum ferritin (ng/ml)	1305.59±1715.62
Diabetes, N (%)	44 (16.5)
LV GCS (%)	-14.74±2.73
LV GRS (%)	22.73±5.76
LV GLS (%)	-14.52±2.26
Global heart T2* (ms)	35.75±11.08
Significant myocardial iron overload, N (%)	32 (12.0)
Number of segments with T2* < 20 ms	2.31±4.84
LV end-diastolic volume index (ml/m2)	85.97±17.23
LV end-systolic volume index (ml/m2)	32.46±11.03
LV mass index (g/m2)	61.39±12.92
LV ejection fraction (%)	62.35±7.07
Abnormal LV motion, N (%)	26 (9.8)
Replacement myocardial fibrosis, N (%)	70/173 (40.5)

TM=thalassemia major, N=number, LV=left ventricular, LV=left ventricular, GCS=global circumferential strain, GRS=global radial strain, GLS=global longitudinal strain.

Table 2. Demographic, clinical, and CMR correlates of left ventricular strain parameters in 266 patients with thalassemia major.

	LV GCS	**LV GRS**	**LV GLS**
Categorical variables			
	Difference of LV strains between two groups (absent vs. present)		
Female sex	-14.16±2.74 % vs. -15.32±2.59 % (p<0.0001)	21.44±5.43 % vs. 23.99±5.82 % (p<0.0001)	-13.96±1.93 % vs. -15.08±2.42 % (p<0.0001)
Splenectomy	-15.05±2.32 % vs. -14.45±3.04 % (p=0.073)	23.49±5.39 % vs. 21.99±6.022 % (p=0.012)	-14.61±2.28 % vs. -14.44±2.25 % (p=0.678)
Diabetes	-14.80±2.57 % vs. -14.45±3.43 % (p=0.527)	22.67±5.39 % vs. 23.01±7.44 % (p=0.634)	-14.67±2.09 % vs. -13.79±2.89 % (p=0.069)
Significant myocardial iron overload	-14.79±2.77 % vs. -14.42±2.35 % (p=0.475)	22.88±5.83 % vs. 21.65±5.21 % (p=0.329)	-14.65±2.22 % vs. -13.59±2.35 % (p=0.017)
Abnormal LV motion	-14.98±2.68 % vs. -12.59±2.21 % (p<0.0001)	23.25±5.66 % vs. 17.88±4.26 % (p<0.0001)	-14.75±2.05 % vs. -12.39±2.92 % (p<0.0001)
LGE	-14.76±2.35 % vs. -14.06±2.60 % (p=0.068)	22.71±5.16 % vs. 21.06±5.55 % (p=0.039)	-14.79±1.95% vs. -13.97±2.59 % (p=0.148)

Cardiac complications	-14.82±2.65 % vs. -13.89±3.39 % (p=0.213)	22.87±5.48 % vs. 21.19±8.27 % (p=0.079)	-14.69±2.05 % vs. -12.64±3.39 % (p=0.006)
Continuous variables			
	Correlation (R, p-value) with LV strains		
Age	R=-0.049, p=0.429	R=0.028 P=0.651	R=0.038, p=0.532
Age at start of regular transfusions	R=0.060, p=0.430	R=-0.106, p=0.164	R=-0.030, p=0.690
Chelation starting age	R=0.058, p=0.459	R=-0.047, p=0.549	R=0.098, p=0.211
Body surface area	R=0.201, p=0.001	R=-0.202, p=0.001	R=0.118, p=0.050
Pre-transfusion hemoglobin	R=-0.014, p=0.828	R=0.015, p=0.814	R=0.047, p=0.474
Mean serum ferritin	R=0.063, p=0.336	R=-0.064, p=0.329	R=0.087, p=0.185
LV GCS		R=-0.950, p<0.0001	R=0.446, p<0.0001
LV GRS	R=-0.950, p<0.0001		R=-0.473, p<0.0001
LV GLS	R=0.446, p<0.0001	R=-0.473, p<0.0001	
Global heart T2*	R=-0.082, p=0.183	R=0.096, p=0.118	R=-0.158, p=0.010

Number of segments with T2* < 20 ms	R=0.093, p=0.129	R=-0.096, p=0.116	R=0.185, p=0.002
LV end-diastolic volume index	R=0.442, p=<0.0001	R=-0.429 p<0.0001	R=0.161, p=0.008
LV end-systolic volume index	R=0.584, p<0.0001	R=-0.578, p<0.0001	R=0.308, p<0.0001
LV mass index	R=0.352, p<0.0001	R=-0.340, p<0.0001	R=0.228, p<0.0001
LV ejection fraction	R=-0.513, p<0.0001	R=0.521, p<0.0001	R=-0.313, p<0.0001

LV=left ventricular, GCS=global circumferential strain, GRS=global radial strain, GLS=global longitudinal strain, N=number, LGE=late gadolinium enhancement.

Table 2. Univariate and multivariate linear regression analysis for the prediction of the LV strain parameters.

	Univariate		Multivariate	
	β	**p-value**	**β**	**p-value**
LV GCS				
Sex	-0.214	<0.0001	-0.214	<0.0001
Age	-0.034	0.583		
Splenectomy	0.109	0.075		
Body surface area	0.133	0.030		
Pre-transfusion hemoglobin	-0.034	0.605		
Mean serum ferritin	0.092	0.159		
Diabetes	0.047	0.442		
LV GRS				
Sex	0.222	<0.0001	0.222	<0.0001
Age	0.021	0.728		
Splenectomy	-0.130	0.034		
Body surface area	-0.151	0.014		
Pre-transfusion hemoglobin	-0.017	0.795		
Mean serum ferritin	-0.090	0.169		
Diabetes	0.022	0.720		
LV GLS				
Sex	-0.247	<0.0001	-0.247	<0.0001
Age	0.052	0.399		
Splenectomy	0.036	0.555		
Body surface area	0.084	0.093		

Pre-transfusion hemoglobin	0.046	0.482
Mean serum ferritin	0.170	0.009
Diabetes	0.145	0.018

LV=left ventricular, GCS=global circumferential strain, GRS=global radial strain, GLS=global longitudinal strain.

FIGURE LEGENDS

Figure 1. Left ventricular strain parameters in healthy subjects and in TM patients.

Figure 2. A) Left ventricular global longitudinal strain in patients without and with significant myocardial iron overload. **B)** ROC curve analysis of left ventricular global longitudinal strain to identify significant myocardial iron overload.

Figure 3. A) Left ventricular global longitudinal strain in patients without and with cardiac complications. **B)** ROC curve analysis of left ventricular global longitudinal strain to detect cardiac complications.