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Role of feature tracking cardiac magnetic resonance imaging in early detection of cardiac dysfunction in β-thalassemia patients recovered from COVID-19: A cross-sectional study

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Abstract

Background and Aims: β-Thalassemia patients may have cardiac complications due to iron overload, which puts them at higher risk of cardiac complications induced by coronavirus disease 2019 (COVID-19) compared with the normal population. The present study aims to evaluate early cardiovascular complications following iron overload in β-thalassemia patients who had early recovery from COVID-19 by cardiac magnetic resonance imaging (MRI) and feature-tracking technique.

Methods: Thirty-two confirmed COVID-19-recovered β-thalassemia cases were evaluated within 3 weeks to 3 months after a positive reverse-transcriptase polymerase chain reaction COVID-19 test. Both the heart and liver of all patients were examined using cardiac MRI.

Results: We analyzed 32 patients with mean age of 32.84 ± 6.45 years at baseline. Left ventricular global strain values were significantly associated with myocardial T2*. A cut-off value of −15.08% for global longitudinal strain (GLS) with sensitivity and specificity of 90% and 61.1% ($p = 0.017$), 32.33% for global radial strain (GRS) with sensitivity and specificity of 80% and 94.4% ($p = 0.001$) and −16.21 for global circumferential strain (GCS), with sensitivity and specificity of 80% and 89.9% ($p = 0.013$) may indicate cardiac iron overload.

Conclusion: GLS, GRS, and GCS were significantly decreased in patients with myocardial T2* <20 ms (iron overload), while no significant change was observed in the right and left ventricular ejection fraction (RV- and LVEF). Cardiac MRI feature-tracking may be helpful in the early detection of cardiac complications resulting from iron overload in β-thalassemia patients who had early recovery from COVID-19.

KEYWORDS

COVID-19, feature tracking, global strain value, T2* value, thalassemia

1 | INTRODUCTION

In December 2019, COVID-19 was identified in Wuhan, China. COVID-19 has rapidly spread globally since being recognized as a public health emergency and has now been declared a pandemic by the World Health Organization (WHO).[1,2] COVID-19 infection is classified based on clinical symptoms into five categories: asymptomatic, mild, moderate, severe, and critical.[3] COVID-19 infection usually starts with flu-like symptoms and can be asymptomatic or may have a mild to severe course.[4,5] The infection is characterized with significant burden of inflammation.[6] Association between inflammation parameters and COVID-19 infection has been well established.[7,8] Thus, studying these markers in β-thalassemia patients recovered from COVID-19 is reasonable. The COVID-19 virus primarily affects the respiratory system, but it has also been reported to cause complications in other organs, including the heart and gastrointestinal tract.[9] Although some mechanisms have been hypothesized for the pathophysiology of cardiac complications, namely direct viral invasion, systematic inflammation, and COVID-19 medications, its underlying mechanisms have not been entirely elucidated.[10] Cardiac involvement in infected COVID-19 patients ranges from a subtle myocardial injury to cardiogenic shock. In a single-center study, the cardiac injury was observed in 19% of hospitalized patients with COVID-19 and was associated with a higher risk of in-hospital mortality.[11] Iron concentration was found significantly elevated in left ventricular myocardium of patients who had died due to COVID-19 which is considered to be related to dysregulation of iron metabolism.[12] Hence, there may be a correlation between iron overload and clinical outcome in these patients. Moreover, patients who had recovered from COVID-19 have higher risk (risk ratio: 3; 95% confidence interval: 2.7–3.2) of developing cardiac dysfunction.[13] Patients with chronic diseases such as thalassemia are at greater risk of developing COVID-19 complications.[14]

β-Thalassemia is the world's most common form of thalassemia.[15] It is characterized with chronic high burden of inflammation.[16] There are two clinical categories of thalassemia disorders: transfusion-dependent β-thalassemia (TDT) and nontransfusion-dependent β-thalassemia (NTDT). β-Thalassemia major as a TDT and β-thalassemia intermedia as a NTDT can cause iron overload due to regular transfusion and increased intestinal absorption, respectively.[17] Both groups of patients may suffer from cardiac complications due to iron overload.[18,19] Therefore, a close cardiovascular surveillance is reasonable, particularly in β-thalassemia patients with increased baseline risk. This baseline risk can be previous cardiovascular comorbidities such as myocardial T2* <20 ms (ms), a personal history of previous or current impaired left ventricular function or a serum ferritin level >2000 ng/mL.[20] Cardiac dysfunction resulting from iron overload becomes clinically manifested only when the disease is at an advanced stage, and it is shown that early diagnosis can make the disease reversible, which declares the importance of early diagnosis.[21,22]

T2* parameter obtained from cardiac magnetic resonance imaging (MRI) can demonstrate tissue iron concentration nonlinearly and allows early detection of myocardial iron overload.[23] Feature tracking by cardiac MRI is capable of providing a more comprehensive evaluation of cardiac contractile ability by expressing longitudinal, circumferential, and radial values.[24] It is stated in several studies that strain values can be associated with myocardial iron overload when assessed with T2* value.[25,26]

Considering the additive effect of β-thalassemia on complications of COVID-19 and iron concentration disorder in both COVID-19 and β-thalassemia, limited data is currently available about the early diagnosis of iron overload-related cardiac complications in β-thalassemia patients following COVID-19. The present study aims to evaluate early cardiovascular complications following iron overload in β-thalassemia major or intermedia patients who had early recovery from COVID-19 by cardiac MRI and feature-tracking technique.

2 | MATERIALS AND METHODS

2.1 | Study design and population

Following the approval of our cross-sectional study method by the Institutional Review Board we recruited consecutive β-thalassemia patients who had early recovery from COVID-19 from June 21, 2021, to March 20, 2022. Early recovery was defined as the opposite of long-COVID-19 which lasts longer than 3 months.[27] According to the Centers for Disease Control and Prevention (CDC), recovered COVID-19 patients have protection for 3 months.[28]

The eligibility criteria were as follows: (1) Patients with β-thalassemia major or intermedia, (2) Patients who had a COVID-19 negative reverse-transcriptase polymerase chain reaction (RT-PCR) test and clinical recovery during 3 weeks to 3 months after a first positive RT-PCR. (3) Patients who signed the ethically approved informed consent to participate in this study. The exclusion criteria were as follows: Patients with (1) minor thalassemia, (2) congenital heart diseases, (3) previous myocarditis, (4) pacemaker placement, (5) Inability to cooperate with breath-holding and to undergo cardiac MRI examination. Eligible cases were evaluated from 3 weeks to 3 months after a positive RT-PCR test.

The patients' clinical characteristics and laboratory findings were collected by visiting and analyzing their medical records. The severity of the COVID-19 disease is classified into five categories: asymptomatic, mild, moderate, severe, and critically ill.[3] Cardiac and liver MRI of patients was performed at the time of study enrollment.

2.2 | Feature tracking cardiac magnetic resonance

Cardiac MRI was performed by a 1.5-T Avanto scanner (Siemens) using electrocardiogram (ECG) gating and a cardiac phased array receiver surface coil. Balanced steady-state free precession (bSSFP) cines were used to acquire vertical, horizontal, and adjacent 10-mm short-axis slices views to cover the entire left ventricle (LV) from the mitral valve plane to the apex (time of repetition [TR] = 3.0–3.5 ms, time of echo [TE] = 1.2–1.5 ms, spatial resolution = 1.8 mm and

temporal resolution = 40 ms). T2* algorithm was performed on the heart and liver with a TE = 1.3–23 ms, TR = 200 ms, the flip angle = 20°, the base resolution matrix = 128 pixels, the field of view = 39.7 cm × 19.7 cm, and the sampling bandwidth = 125 kHz.[29] Myocardial T2* <20 ms value was reported as a myocardial iron overload.[30] For the liver, a region of interest (ROI) was drawn in a homogeneous parenchyma region and T2* <6.3 ms value was reported as a liver iron overload.[31] Long axis planes (two-, three-, and four-chamber) were used to calculate global longitudinal strain (GLS). Short-axis plane was used to evaluate circumferential and radial strain (GCS and GRS).

All data were evaluated retrospectively using CMR42 (Circle Cardiovascular Imaging Inc.).

2.3 | Ethical approval

The Ethics Committee of Tehran University of Medical Sciences approved the design and conduct of the study. The study was performed in accordance with Helsinki Declaration.

2.4 | Statistics

Statistical analysis was performed using SPSS 26 (SPSS Inc.). Categorical variables were expressed as percentages and continuous variables as mean ± SD. The normality of distribution was tested using the Shapiro–Wilk test. An independent *t*-test was used to compare the means of numerical variables. Qualitative data were compared with Fisher's exact test. Pearson correlation test was performed to evaluate the correlation between strain groups and T2*. The receiver operating characteristic (ROC) curve was used to establish the best cut-off values of GLS, GCS, and GRS to determine the myocardial iron overload and the sensitivity and specificity of those values. All tests were one-sided. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

In this study, 32 patients with β-thalassemia who had early recovery from COVID-19 were recruited from June 21, 2021, to March 20, 2022. The clinical characteristic of patients is shown in Table 1. Based on the previous classification, the numbers of infected patients in each group were as follows: mild ($n = 15$), moderate ($n = 11$), and severe or critical ($n = 6$). There was a significant association between liver T2* and serum ferritin level ($p < 0.001$). A significant association was observed between serum ferritin level and myocardial T2* ($p = 0.03$).

3.2 | MRI and feature-tracking imaging

Based on normal range of myocardial T2*, 37.5% ($n = 12$) had cardiac (T2* < 20 ms) and 78.1% ($n = 25$) had liver (T2* < 6.3 ms) iron overload.

TABLE 1 Clinical characteristics of patients based on myocardial T2*.

Characteristic	All patients ($n = 32$)	T2* < 20 ms ($n = 13$)	T2* > 20 ms ($n = 19$)	*p* Value
Age	32.84 ± 6.45	30.46 ± 4.96	34.47 ± 6.96	0.08
BSA (m^2)	1.67 ± 0.16	1.67 ± 0.17	1.68 ± 0.16	0.82
Serum ferritin (ng/mL)	1895.09 ± 2040.38	2947.77 ± 2502.31	1174.84 ± 1283.58	**0.03**
Hemoglobin (mg/dL	9.35 ± 1.17	9.66 ± 1.28	9.14 ± 1.07	0.22
Gender				>0.99
Female, no. (%)	16 (50%)	7 (53.8%)	9 (47.4%)	
Male, no. (%)	16 (50%)	6 (37.5%)	10 (62.5%)	
Thalassemia				0.06
Intermedia, no. (%)	5 (15.6%)	0	5 (26.3)	
Major, no. (%)	27 (84.4%)	13 (100%)	14 (73.7%)	
Transfusion dependant				0.25
TDT	29 (90.6%)	13 (100%)	16 (84.2%)	
NTDT	3 (9.4%)	0	3 (15.8%)	
Admission for COVID-19, no. (%)	7 (21.9%)	3 (23.1%)	4 (21.1%)	>0.99

Note: *p* Values < 0.05, which are considered statistically significant, are bolded in the table.

Abbreviations: BSA, body surface area; NTDT, nontransfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia.

No significant association was observed between the severity of COVID-19 and cardiac (T2* < 20 ms) and liver (T2* < 6.3) iron overload.

None of the MRI parameters, except strain values, were significantly associated with the severity of COVID-19. Both myocardial and liver T2* results are summarized in Table 2. All three strain parameters (GCS, GRS, and GLS) were significantly lower in patients with myocardial T2* < 20 ms ($p < 0.05$). Based on ROC curve analysis, a GRS ≤ 32.33% with 80% sensitivity and 94.4% specificity (area under the curve, AUC = 0.889, $p = 0.001$), a GLS ≤ 15.08% (≥−15.08) with 90% sensitivity and 61.1% specificity (AUC = 0.778, $p = 0.017$) and a GCS ≤ 16.21 (≥−16.21) with 80% sensitivity and 89.9% specificity (AUC = 0.789, $p = 0.013$) could predict myocardial iron overload (T2* < 20 ms) (Figure 1). An example of strain imaging showing iron overload is shown in Figure 2.

4 | DISCUSSION

To the best of our knowledge, this is the first study to assess cardiac MRI-derived strain parameters in β-thalassemia patients who had early recovery from COVID-19. Patients with chronic diseases such as β-thalassemia are more likely to develop COVID-19 complications. Feature-tracking as a novel promising cardiac MRI technique is a promising tool for detecting early changes in myocardial dysfunction.

Dysregulation of iron metabolism and iron deposition in left ventricular myocardium of patients is hypothesized to be related to mortality in patients who have recovered from COVID-19.[12] This iron accumulation is found to be intracellular and is associated with decreased iron storage capacity, inhibition of antioxidant enzymes, and activation of the ferroptosis pathway, a newly discovered type of apoptosis, resulting in increased myocardial oxidative stress and hence, myocardial damage.[12] Patients with chronic diseases such as thalassemia are at greater risk of developing COVID-19 complications such as cardiac disorders.[14] TDT and NTDT can cause iron overload due to regular transfusion and increased intestinal absorption, respectively.[17]

In this study, we assessed the correlation of serum ferritin level and cardiac MRI imaging findings in β-thalassemia patients who had early recovery from COVID-19 with the findings of myocardial T2* as the best indicator of cardiac iron overload. Serum ferritin level was significantly associated with both myocardial and liver T2*. Among cardiac MRI findings, GLS, GCS, and GLS were significantly associated with myocardial T2*, and patients with T2* < 20 ms had significantly lower strain values. The rest of the cardiac MRI findings were not significantly associated with myocardial T2* and hence were insufficient for predicting cardiac iron overload or dysfunction. ROC analysis shows a cut-off value of −15.08% for GLS (90% sensitivity and 61.1% specificity), 32.33% for GRS (80% sensitivity and 94.4% specificity), and −16.21% for GCS (80% sensitivity and 89.9% specificity). Despite previous studies in β-thalassemia patients, we found a significant correlation between all three cardiac MRI-derived strain parameters (GLS, GRS, and GCS) and myocardial T2*. In a study by Rezaeian et al., it was shown that MRI-derived GLS and GCS have a significant correlation with myocardial T2*. They also found a significant difference in GLS between patients with iron overload (T2* < 20 ms) and those without (T2* > 20 ms). They suggested a GLS value of less than 16.5% to predict T2* < 20 ms with 73% sensitivity and 63% specificity.[32] In another study by Ojha et al., MRI-derived GRS was correlated with myocardial T2*,

TABLE 2 Cardiac MRI characteristics of the patients based on myocardial T2* value.

Characteristics	All patients ($n = 32$)	T2* < 20 ($n = 12$)	T* > 20 ($n = 20$)	p Value
LVEF	50.15 ± 10.98	49.83 ± 11.40	56.40 ± 2.90	0.07
LVEDV	93.07 ± 17.23	93.00 ± 18.00	90.08 ± 20.21	0.68
LVESV	47.15 ± 16.72	47.50 ± 17.41	38.96 ± 9.05	0.13
LVSV	50.36 ± 13.20	48.40 ± 14.16	51.17 ± 9.79	0.51
LVMI	95.63 ± 28.44	45.72 ± 13.41	42.98 ± 11.75	0.55
RVEF	50.81 ± 31.32	50.36 ± 13.20	54.16 ± 7.66	0.39
RVESV	45.50 ± 12.81	50.81 ± 31.32	44.00 ± 14.17	0.50
RVEDV	48.60 ± 13.58	95.63 ± 28.44	91.00 ± 22.02	0.62
GLS	−11.44 ± 3.53	−12.46 ± 3.10	−15.20 ± 2.47	**0.01**
GCS	−14.90 ± 3.71	−14.61 ± 3.78	−17.93 ± 2.04	**0.005**
GRS	27.93 ± 8.21	27.41 ± 8.46	40.11 ± 7.55	**<0.001**
Liver T2*	3.79 ± 3.42	3.60 ± 3.50	5.17 ± 4.69	0.32

Note: p Values < 0.05, which are considered statistically significant, are bolded in the table.

Abbreviations: GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; LVSV, left ventricular stroke volume; MRI, magnetic resonance imaging; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.

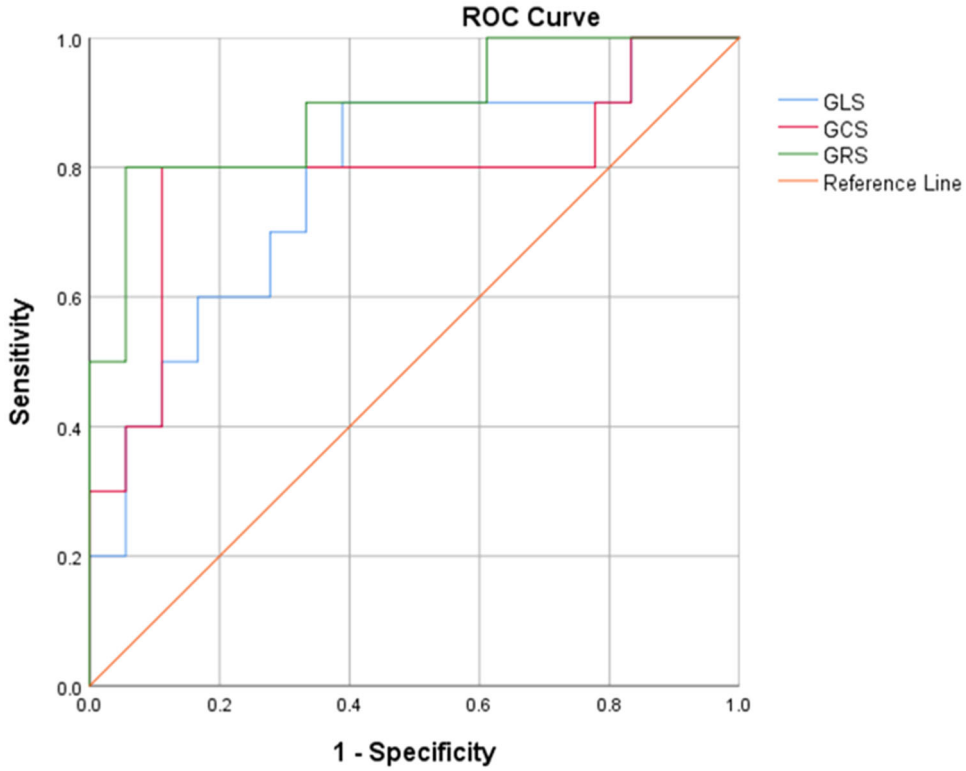

FIGURE 1 Receiver operating characteristic curve analysis results based on myocardial strains. GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; ROC, receiver operating characteristic.

and a GRS value of less than 29.3% was suggested to predict T2* < 20 ms with 76.5% sensitivity and 66.7% specificity.[24] In a study by Abtahi et al., they revealed a significant correlation between echocardiography-derived GLS and myocardial T2*. They suggested a GLS value of less than 19.5% to predict T2* < 20 ms with 82.14% sensitivity and 86.36% specificity. They also did not find any correlation between serum ferritin and myocardial T2* level.[20]

As stated by Claus et al., temporal averaging may be a reason why echocardiography-derived strain values are larger than cardiac MRI-derived ones.[33] As noted before, our study is the first among β-thalassemia patients that found a significant association between all three cardiac MRI-derived strain parameters and myocardial T2* value. It may be due to the cardiac complications of COVID-19. In a study by Wang et al., a significant decrease was seen in cardiac MRI-derived LV GCS and RV GCS and GLS in COVID-19-affected patients compared to normal controls.[34] In several studies, cardiac MRI and echocardiography have demonstrated RV dysfunction in COVID-19 survivors.[35–37] Same as in a study by Heris et al., we found a significant correlation between serum ferritin level and cardiac iron overload (T2* < 20 ms).[38] As noted in studies by Chowdhury et al. and Mahroum et al., 4 weeks to 3 months after recovery from COVID-19, serum ferritin level, as an acute phase reactant protein, was significantly above normal level.[39,40] Hence, in this study, it is unclear whether the increase in serum ferritin level is a result of iron overload or a previous COVID-19 infection; and it cannot be used as a predictor for iron overload in these patients. Further studies with a more extended investigation on inflammation may clarify the main reason for the ferritin raise. Our study shows a significant association between cardiac MRI-derived LV strain values (GLS, GCS, and GRS) and myocardial iron overload (T2* < 20 ms); meanwhile, the RV- and LVEF did not show a significant association with myocardial T2*. It was in agreement with the results of the study by Parsaee et al., which suggested an echocardiography-derived GLS value less than 18.5% with 73% sensitivity and 63% specificity to predict myocardial T2* < 20 ms while the LVEF amount was not predictive.[31] Considering the results, strain values may be better predictors for iron overload than serum ferritin level in these patients.

In this study, we investigated strain values using cardiac MRI in COVID-19-recovered patients who have β-thalassemia. As far as we know, this the first study to investigate this problem. This study suggests strain cut-offs to detect myocardial iron overload and disorders. By these cut-offs not only we can detect early iron deposition, but also early myocardial incompetency. Considering the on-going risk of developing new COVID-19 variants, this can help preventing one major cause of mortality in these patients. Results of this study can be used to be compared with COVID-19-recovered patients without accompanying β-thalassemia.

This study had multiple limitations that should be considered when interpreting its findings. Image quality is a limiting factor in cardiac MRI. Also, because we only investigated patients who had early recovery from COVID-19, the results do not apply to patients who are currently infected or did not recover early. The COVID-19

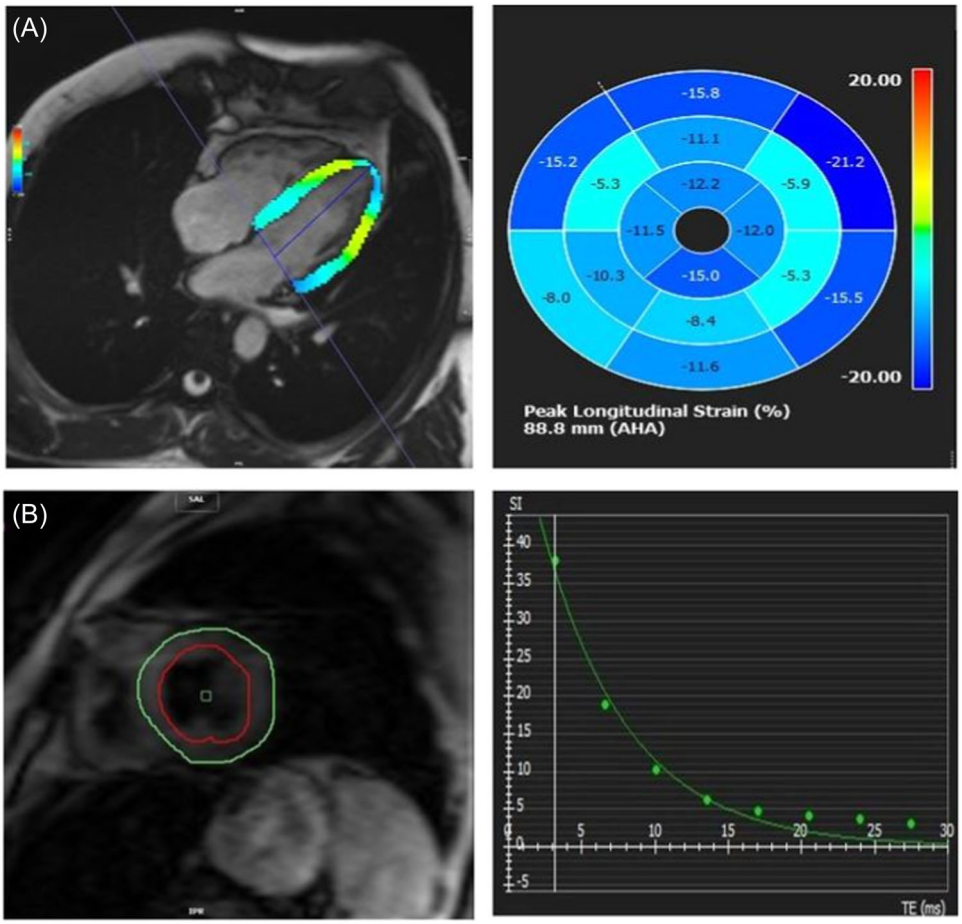

FIGURE 2 Cardiac strain analysis. (A) Decreased global longitudinal strain of left ventricle; bull's eye representation of the peak values of longitudinal strain. (B) A patient with β-thalassemia major. GRE short axis sequence of the heart shows T2* value equal to 5.93 ± 0.58 ms (R = 0.975), indicating iron overload. GRE, gradient recalled echo.

pandemic was a limiting factor for which we tried keeping not-infected β-thalassemia patients away from the COVID-19 virus. Also, the cardiac studies were performed in a cardiologic research hospital, which prevented the inclusion of many hospitalized and acute-stage patients. In addition, the study did not include asymptomatic patients or patients who didn't undergo RT-PCR testing and were cured with conventional home care. Further studies with larger study populations and reduced limitations are needed.

5 | CONCLUSION

Cardiac MRI feature-tracking may be helpful in the early detection of cardiac complications resulting from iron overload in β-thalassemia patients who had early recovery from COVID-19. It was shown in this study that a decrease in GRS, GLS, and GCS can detect cardiac dysfunction before a significant change in RV- or LVEF. Cardiac MRI feature-tracking may be helpful in the early detection of cardiac complications resulting from iron overload in β-thalassemia patients who had early recovery from COVID-19.

AUTHOR CONTRIBUTIONS

Golnaz Houshmand: Conceptualization; investigation; writing—original draft; writing—review and editing; project administration. **Mozhgan Parsaee**: Methodology; investigation; formal analysis. **Leila Najmafshar**: Investigation; formal analysis; writing—review and editing. **Nadia Rajablou**: Writing—original draft; writing—review and editing; formal analysis. **Hasti T. Golroudbari**: Writing—original draft; writing—review and editing. **Rana Hosseini**: Writing—review and editing; supervision. **Negar Omidi**: Supervision; data curation; resources; formal analysis; writing—review and editing; visualization; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available on a reasonable request from the corresponding author.

ETHICS STATEMENT

Informed consent was obtained from all individual participants included in the study.

TRANSPARENCY STATEMENT

The lead author Negar Omidi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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