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Original Article

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Magnetic Resonance Myocardial Feature Tracking in Transfusion-Dependent Myelodysplastic Syndrome

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ABSTRACT

BACKGROUND: Myocardial deformation with echocardiography allows early detection of systolic dysfunction and is related to myocardial iron overload (MIO) determined by T2* in hereditary anemias under transfusion support. Our aim was to analyze the diagnostic and prognostic usefulness of magnetic resonance feature tracking (MR-FT) myocardial strain in low-risk myelodysplastic syndromes (LR-MDS) patients.
METHODS: Prospective study in transfusion-dependent LR-MDS patients and healthy controls who underwent a cardiac MR-FT. We analyzed the relationships between strain MR-FT and iron overload parameters and its prognostic impact in cardiovascular events and/or death.
RESULTS: Thirty-one patients and thirteen controls were included. MIO (T2* < 20 ms) was detected in 9.7% of patients. Left ventricular global longitudinal strain (LV-GLS) by MR-FT was pathological (> –19.3%) in 32.3% of patients. Less negative strain values correlated with lower T2* (R = −0.37, p = 0.033) and native myocardial T1 (R = −0.39, p = 0.031) times. LV-GLS by MR-FT was significantly associated with higher incidence of the combined cardiovascular events and/or all-cause death (p = 0.047), with a cut-off value of –17.7% for predicting them (63% sensitivity and 81% specificity, area under the curve = 0.69). After adjusting analysis including demographic, biomarkers and imaging variables, a higher LV-GLS value by MR-FT remained as predictor of combined event in transfusion-dependent LR-MDS patients (hazard ratio, 0.4; confidence interval, 0.15–0.98; p = 0.045).
CONCLUSIONS: Longitudinal myocardial strain by MR-FT in LR-MDS patients is associated to MIO and correlates with adverse events in the follow-up, what could serve as a prognostic tool.

Keywords: Myelodysplastic syndrome; Iron overload; Cardiac magnetic resonance; Feature tracking; Myocardial deformation

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological disorders characterized by peripheral cytopenias and an increasing risk of evolution into acute myeloid leukemia. Cardiovascular disease is an important cause of morbimortality in MDS patients.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Alonso-Fernandez-Gatta M, Martin-Garcia A; Formal analysis: Alonso-Fernandez-Gatta M, Martin-Garcia A; Funding acquisition: Martin-Garcia A; Investigation: Alonso-Fernandez-Gatta M, Martin-Garcia A, Diez-Campelo M; Methodology: Alonso-Fernandez-Gatta M, Martin-Garcia A, Barreiro-Pérez M, Lopez-Cadenas F, Diaz-Pelaez E; Project administration: Martin-Garcia A; Resources: Alonso-Fernandez-Gatta M, Martin-Garcia AC, Barreiro-Pérez M, Diaz-Pelaez E; Software: Barreiro-Pérez M; Supervision: Diez-Campelo M, Sanchez PL; Validation: Alonso-Fernandez-Gatta M, Martin-Garcia A, Diez-Campelo M, Martin-Garcia AC, Barreiro-Pérez M, Lopez-Cadenas F; Visualization: Alonso-Fernandez-Gatta M; Writing - original draft: Alonso-Fernandez-Gatta M; Writing - review & editing: Alonso-Fernandez-Gatta M, Martin-Garcia A, Diez-Campelo M, Martin-Garcia AC, Lopez-Cadenas F, Diaz-Pelaez E, Sanchez PL.

They have a high incidence of cardiovascular events (between 20–70% depending on the series)[1)2)] and heart disease is their second cause of death.[3)]

Iron overload cardiomyopathy (IOC) is a frequent condition secondary to repeated red blood cell (RBC) transfusions. Prevalence of IOC in transfusion-dependent MDS patients ranges between 7–16%.[4)] Those patients belonging to low-risk groups, due to their better prognosis, have a higher risk of developing IOC since they receive transfusion support for a longer time. The development of systolic dysfunction and heart failure (HF) is generally a late event that shows a dismal prognosis despite treatment with iron chelators (ICh).[5)] Thus, its early detection is crucial for establishing the ICh therapy, which has demonstrated an increase in event-free survival of the combined death and non-fatal event (related to cardiac and liver function or leukemia transformation) compared to placebo in low-risk MDS patients under transfusion support.[6)]

Myocardial iron overload (MIO) must be diagnosed with cardiac imaging techniques, because iron overload serum markers (ferritin and labile plasma iron) and/or the presence of hepatic siderosis do not correlate adequately with cardiac siderosis.[7)8)] T2* relaxation time measured by cardiac magnetic resonance (cMR) has become the gold standard parameter for the diagnosis and follow-up of these patients,[9)] which is reduced in the presence of intramyocardial ferritin and hemosiderin.

Myocardial deformation or strain is an evolving tool to quantify regional and global myocardial function, detecting subclinical dysfunction and providing prognostic information in several pathologies.[10)] The 2-dimensional speckle tracking imaging (2DSTI) strain by echocardiography allows early detection of systolic dysfunction and is related to myocardial T2* in hereditary anemias under transfusion support (*i.e.*, thalassemia).[11)12)] Myocardial deformation by magnetic resonance feature tracking (MR-FT) allows revealing subclinical states of different heart diseases, with better image quality and reproducibility than echocardiography.[13)]

Currently, it is unknown the usefulness of other myocardial deformation analysis techniques such as MR-FT in hematological malignancies requiring chronic transfusions.

Therefore, our aim was to analyze the usefulness of MR-FT myocardial strain in patients with low-risk MDS under chronic RBC transfusions, to explore its relationship with MIO, and to assess its prognosis value.

METHODS

Study population

Prospective observational study IRON-HEART-SMD (*EvaluacIón de la caRdiotOxicidad por depósito de hierro en pacíeNtes HEmAtológicos con síndRome mielodisplásico de bajo grado: uso de nuevas Técnicas de imagen*) in low-risk MDS patients.

Between January 2016 and February 2017, we included consecutive patients with very low, low and intermediate risk category of the Revised-International Prognostic Scoring System (IPSS-R),[14)] under chronic transfusion support of RBC, over the age of 18. They were followed to determine the incidence of the combined event, defined as cardiovascular event (new diagnosis of ischemic heart disease, HF or arrhythmias) and/or mortality (all causes).

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As a control group to compare the MR results, thirteen elderly patients (over 65 years old) without heart disease were selected and cMR with the same protocol was performed.

This study was conducted in accordance with Helsinki Declaration, acquired the Institutional Review Board and research ethics board approval, and all patients gave their authorization by signing informed consent.

cMR: acquisition and analysis

cMR was performed in all patients. cMR examinations were conducted with a Philips 1.5-Tesla Achieva whole-body scanner (Philips Healthcare, Amsterdam, The Netherlands) equipped with a 16-element phase-array cardiac coil and simultaneous electrocardiogram gating, using gadolinium contrast.

The study included sequences to assess cardiac morphology and function: steady-state free precession (SSFP) end-expiratory breath-hold cines in long (standard 2-chamber, 4-chamber and 3-chamber views) and short axis planes. Post-processing was carried out by an observer with extended experience in MR. Diameters, volumes, mass and regional and global functions of left ventricle (LV) and right ventricle (RV) were quantified following the standard recommendations[15)16)] using the software Intelli Space Portal (Philips Healthcare).

We performed tissue characterization by late gadolinium enhancement, T1 and T2* mapping. The acquisition of T2* relaxation time was carried out by multi-echo gradient sequences, with an inversion time that suppresses the intracavitary blood signal, with up to 15 different echo times from 1 to 16 milliseconds. Native T1 acquisition was performed with a modified look locker inversion recovery (MOLLI) sequence with-5(3)3 scheme. T2* and native T1 were calculated using the software Medis suite 2.1 (Medis Medical Imaging Systems, Leiden, The Netherlands) by drawing the ROI or "region-of-interest" in the mid-septum segment in LV short axis. We defined MIO as T2* time < 20 ms.[15)] We considered normal T1 times those extracted from 292 controls without heart disease performed using the same technique (993 ± 62 ms). Scan parameters were described in **Supplementary Data 1**.

Myocardial deformation was assessed using the dedicated software Qstrain 2.0 feature-tracking package (Medis Medical Imaging Systems), that allows the measurement of 2D strain derived parameters based on the tracing of the myocardial borders on standard cine SSFP images acquired prior to contrast administration.[17)] Quantification of parameters was performed by expert cardiologist with extended experience in MR. They were calculated the LV global longitudinal strain (GLS) from the average of three standard long-axis cine views, global circumferential strain (GCS) and global radial strain (GRS) from the three short-axis views (basal, mid and apical LV slices), and RV GLS in 4-chamber view (**Figure 1**). Endocardial and epicardial borders were manually drawn in all short-axis cines, excluding papillary muscles from the endocardial contour. In long-axis direction, it was only required to delimit the endocardial contour. They were traced on the end-diastolic images and one end-systolic image, with subsequent automated tracking of the contours over the remainder of the images. A semi-automated tracking algorithm was applied in all the cine sequences throughout the cardiac cycle and then was visually reviewed and manually adjusted if necessary. We considered pathological values those reported in the literature.[18)]

LV-GLS by MR-FT results were compared to 2DSTI analysis by echocardiography. LV-GLS by echocardiography postprocessing was performed with QLAB software (Philips Healthcare)

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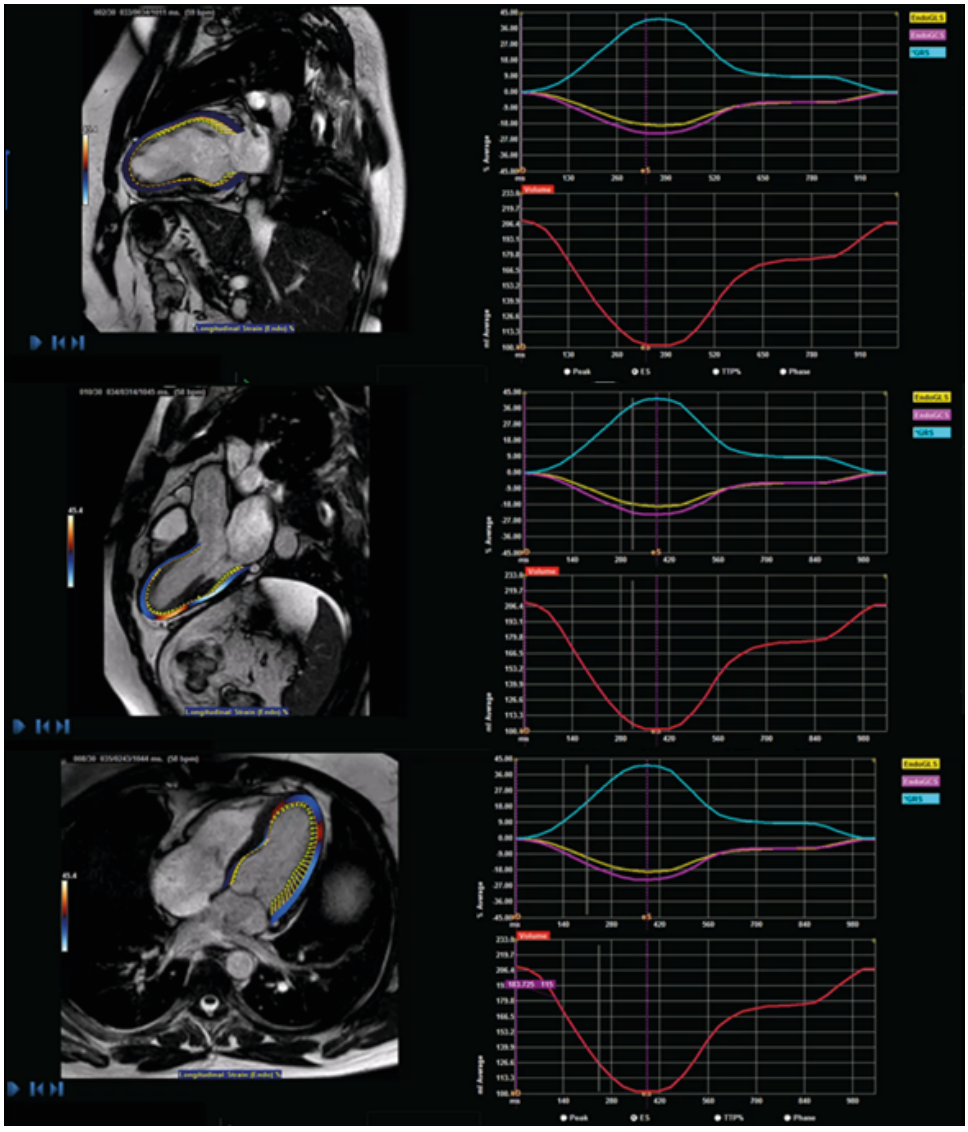

Figure 1. Measurement of LV-GLS feature tracking.
Post-processing cine steady-state free precession images to obtain LV-GLS from the average of three standard long-axis views.
Abbreviations: LV-GLS=left ventricular global longitudinal strain.

derived from 3 long-axis apical views following the same methodology previously described for cMR.

Statistical test

Analyses were performed using SPSS package, version 22.0. Qualitative variables were expressed as absolute number and percentage (%) and continuous values were reported as mean ± standard deviation (SD) or median and interquartile range depending on their normal or not distribution.

Differences in MR results between patients and controls as well as LV-GLS by MR and echocardiography results were compared using χ^2 or Fisher's exact tests and Student's t-test or U Mann-Whitney test where appropriate. Correlations between different clinical, analytical

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and MR parameters with strain results were evaluated using Pearson's or Spearman's correlation coefficient.

We analyzed the prognostic value of MR-FT myocardial deformation for the combined event. Receiver operating characteristic (ROC) curve was used to establish the best-cut off value of LV-GLS predicting the combined event. Kaplan-Meier methods were used to evaluate the relationship between LV-GLS and time to combined event.

Finally, we performed a multivariate cox-regression analysis including demographic, biomarkers and imaging characteristics to study the independent prognostic value of LV-GLS predicting the combined event.

A p value of < 0.05 was considered statistically significant for all analysis.

RESULTS

Baseline characteristics of study population

Out of 36 patients with low-risk MDS recruited from 2016 to 2017, 31 of them were transfusion-dependent, constituting the study population. They were old patients with 76 ± 10 years mean age, 55% males, and 64.5% were receiving ICh. Most of them (93.5%) had cardiovascular risk factors and 38% suffered background of heart disease, but only 6.5% had a previous HF diagnosis (**Table 1**). **Table 1** summarizes baseline, hematological and heart disease characteristics of patients.

The healthy control group (all of them over 65 years old) were younger than MDS patients (68.7 ± 3 vs. 76.9 ± 9, p < 0.001) and did not present anemia (mean hemoglobin in controls 15 ± 1 vs. 9.3 ± 2 in MDS patients, p < 0.001) nor previous heart disease.

cMR results

CMR could be performed in 31 patients under chronic transfusion requirement. The morphological and functional study detected high prevalence of unknown structural heart disease (51.6% had some alteration): almost one third of patients had left and right ventricular dilatation (27.6% and 31% respectively), 20.7% left and 6.4% right systolic dysfunction, 6% ischemic subendocardial late enhancement, 51.6% and 12.9% left and right atria enlargement respectively, 18% valve disease (≥ moderate grade) and 17.2% mild pericardial effusion. They showed larger ventricles and atria dimensions and LV mass, but similar systolic function than controls (**Table 2**).

MIO (T2* < 20 ms) was detected in 3 (9.7%) patients and 13 (41.9%) individuals had hepatic iron overload (T2* < 6.4 ms). Five patients (16.1%) had lower native T1 times than those considered normal in our control group (< 932 ms). All patients with reduced myocardial T2* showed decreased value of native T1 relaxation time.

Different parameters of myocardial deformation calculated by MRI-FT could be performed in all patients (**Table 2**). Almost a third of MDS patients presented a pathological value of LV-GLS and half of them impaired LV-GCS, although only 20% of them had low left ventricular ejection fraction (LVEF). MDS patients had lower LV-GLS (−20.2 ± 2.3% vs. −27.9 ± 4.6%, p < 0.001) and lower LV-GCS (−20.7 ± 6.9 vs. −24.1 ± 3, p = 0,038) than healthy controls, despite

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Table 1. Baseline characteristics, hematological and cardiac situation at inclusion (n = 31)

Baseline characteristics	Values
Age (year)	76 ± 10
Sex (male)	17 (54.8)
MDS WHO2017	
MDS-RS-SLD	6 (19.4)
MDS-RS-MLD	10 (32.3)
MDS-SLD	2 (6.5)
MDS-MLD	9 (29.0)
MDS with excess blasts-1	2 (6.5)
MDS associated with isolated del (5q)	2 (6.5)
MDS evolution (year)	3.9 ± 3.5
Number of red blood cell units transfused	47 [286]
Transfusion burden	
Low (< 25 RBC)	10 (32.3)
Medium (25–125 RBC)	12 (38.7)
High (> 125 RBC)	9 (29.0)
Iron chelation treatment	20 (64.5)
Hemoglobin level (g/dL)	8.9 ± 1.7
Ferritin level (ng/mL)	1,469 [5,739]
NT-proBNP value (pg/mL)	476 [577]
High-sensitive T troponine value (pg/mL)	15 [5.3]
CVRFs	
≥ 1 CVRF	29 (93.5)
Arterial hypertension	18 (58.1)
Diabetes mellitus	5 (16.1)
Dyslipidemia	6 (19.4)
Active or previous smoking	9 (29.0)
Obesity	5 (16.1)
Previous cardiac disease	
Total	12 (38.7)
Ischemic cardiopathy	6 (19.4)
Myocardial infarction	3 (9.7)
Arrhythmias	7 (22.6)
Heart valve disease ≥ moderate	5 (16.1)
Systolic dysfunction	2 (6.5)
Heart failure	2 (6.5)
Pacemaker	0 (0.0)
Cardiovascular treatment	
Antiplatelet therapy	8 (25.8)
Anticoagulation	5 (16.1)
Diuretic	16 (51.6)
ACE inhibitors/ARBs	10 (32.3)
Beta-blocker	5 (16.1)
Digoxin	1 (3.2)
Statins	5 (16.1)

Qualitative variables were expressed as number (%) and continuous values were reported as mean ± standard deviation or median and interquartile range depending on their normal or not distribution.
ACE: angiotensin-converting enzyme, ARBs: angiotensin-II receptor antagonists or blockers, CVRF: cardiovascular risk factor, MDS: myelodysplastic syndrome, MLS: multilineage dysplasia; NT-proBNP: N-terminal pro b-type natriuretic peptide, RBC: red blood cell, RS: ring sideroblasts, SLD: single lineage dysplasia, WHO: World Health Organization.

similar LVEF (63.6% vs. 68%, p = 0.109). All patients had a normal LV-GRS (> 28.5%), with an 86.9 ± 30% mean value, without significant differences regarding controls (83.8 ± 28 vs. 83.5 ± 39, p = 0.985). RV-GLS was pathological (> −20.2%) in 6.4% of patients.

LV-GLS by echocardiography could be analyzed in 71% of patients; the rest of cases could not be properly processed due to the acoustic window. We did not find significant differences regarding the detection of pathological LV-GLS by echocardiogram and CMR (18.2% vs. 32.3%, p = 0.937).

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Table 2. Cardiac magnetic resonance main results in transfusion dependent MDS patients compared to controls

Cardiac magnetic resonance main results	Patients (n = 31)	Controls (n = 13)	p-value
LV end-diastolic volume (mL)	155 ± 49	111 ± 17.1	< **0.001**
LV end-systolic volume (mL)	59 ± 35	34.5 ± 8.3	**0.001**
LV mass (g)	125 ± 36	91 ± 11.9	< **0.001**
RV end-diastolic volume (mL)	141 ± 39	103 ± 18	< **0.001**
RV end-systolic volume (mL)	54 ± 22	35 ± 7.8	**0.001**
LV ejection fraction (%)	63.6 ± 10.7	68.2 ± 6.5	0.109
RV ejection fraction (%)	65.6 ± 6.6	66.2 ± 6.3	0.764
Left atria area (cm^2)	29.2 ± 7	18.5 ± 3.5	< **0.001**
Right atria area (cm^2)	23.4 ± 8.2	16.8 ± 2.7	**0.008**
Septal myocardial T2* time (ms)	32.8 ± 8.8	33.8 ± 2.7	0.415
T1 native mapping (ms)	995 ± 84	988 ± 31	0.729
Hepatic T2* time (ms)	7.1 ± 7.8	20.23 ± 8.5	< **0.001**
LV GLS FT (%)	−20.2 ± 2.3	−27.9 ± 3	< **0.001**
LV GCS FT (%)	−20.7 ± 6.9	−24.1 ± 3	**0.038**
LV GRS FT (%)	83.8 ± 28	83.5 ± 39	0.985
RV GLS FT (%)	−28.1 ± 5.1	−24.3 ± 3	**0.004**
Pathological strain value			
LV GLS FT (> −19.3%)	10 (32.3)	0 (0.0)	**0.021**
LV GCS FT (> −21.7%)	15 (48.4)	0 (0.0)	**0.002**
LV GRS FT (< 28.5%)	0 (0.0)	0 (0.0)	1.000
RV GLS FT (> −20.2%)	2 (6.5)	0 (0.0)	1.000

Qualitative variables were expressed as number (%) and continuous values were reported as mean ± standard deviation. Bold-faced p-value < 0.05 was considered significant.
FT: feature tracking, GCS: global circumferential strain, GLS: global longitudinal strain, GRS: global radial strain, LV: left ventricle, MDS: myelodysplastic syndrome, RV: right ventricle.

Figure 2 shows three examples of cMR multimodality approach in low-risk MDS patients.

MR-FT myocardial deformation parameters correlations

The LV-GLS value by MR-FT correlated significantly with morphological and functional parameters such as higher LV end-systolic volume (R = 0.48, p = 0.008), lower left and right ventricular ejection fraction (R = −0.70, p < 0.001 and R = −0.54, p = 0.004 respectively), and higher N-terminal pro b-type natriuretic peptide (NT-proBNP) value (R = 0.5, p = 0.005).

Moreover, LV and RV GLS correlated significantly with lower septal T2* (R = −0.37, p = 0.033 and R = −0.48, p = 0.009, respectively; **Figure 3**) and LV-GLS correlated with native myocardial T1 (R = −0.39, p = 0.031) times, parameters that are fundamental in MIO detection. We did not find this relationship between T2* and native T1 and GRS (T2*: R = 0.256, p = 0.189; T1: R = 0.099, p = 0.630) or GCS (T2*: R = −0.301, p = 0.119; T1: R = −0.041, p = 0.841). However, none of strain parameters were correlated with transfusion burden (LV-GLS: R = 0.12, p = 0.52; GRS: R = −0.12, p = 0.95; GCS: R = 0.074, p = 0.69) or serum ferritin levels (LV-GLS: R = 0.164, p = 0.36; GRS: R = 0.78, p = 0.67; GCS: R = 0.11, p = 0.54).

LV-GLS did not correlate with variables such as age (p = 0.148), sex (p = 0.876), or cardiovascular risk factors (arterial hypertension p = 0.208, diabetes p = 0.857, and dyslipidemia p = 0.932). In the regression analysis with adjustment for these covariates, the correlation between the myocardial T2* and LV-GLS maintained a trend towards statistical significance (p = 0.062).

MR-FT myocardial deformation and the combined event

After a median follow up of 2.2 years (0.44), 11 (35.5%) patients died and/or suffered a cardiovascular event. 5 patients (16%) died, 4 of them because of a non-cardiovascular cause

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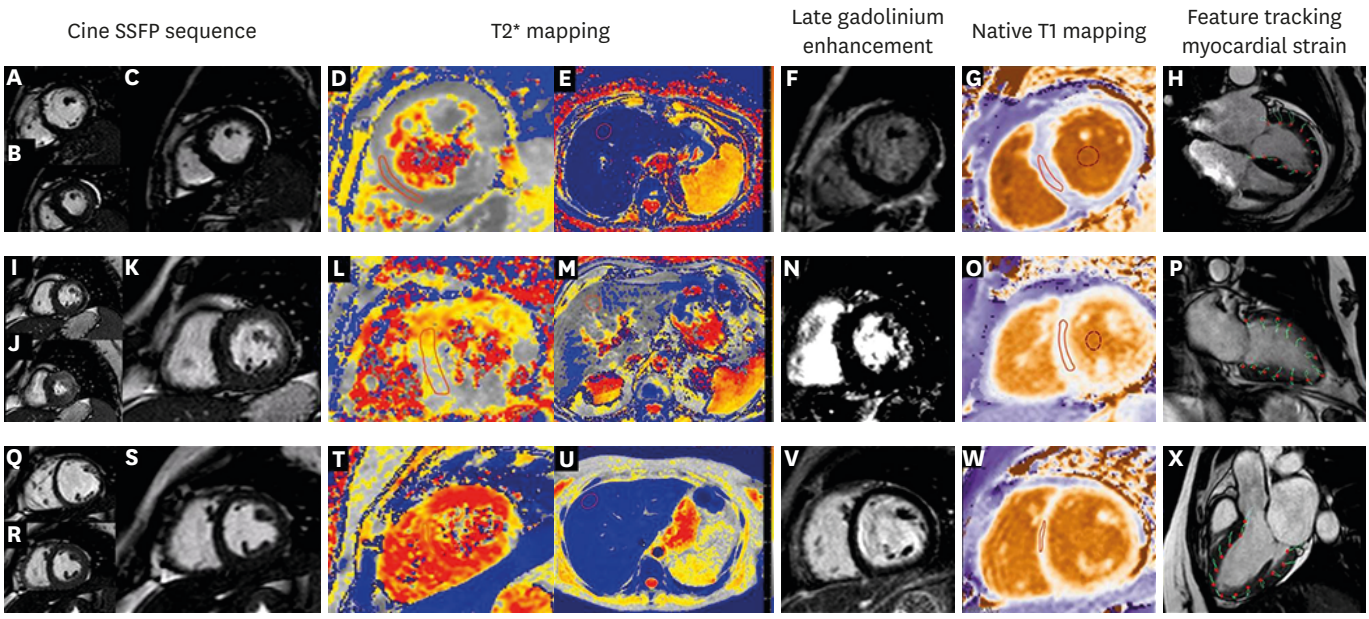

Figure 2. Examples of cMR multimodality approach in low-risk myelodysplastic syndrome patients.
From left to right images show results of cMR multimodal approximation: SSFP short-axis view, myocardial and hepatic T2*, LGE, native T1 mapping, and LV-GLS by feature tracking.
Patient with non-dilated LV (A: diastole, B: systole) and normal LVEF 57% (C: associated Movie 1), reduced myocardial T2* 8 ms (D) and hepatic T2* 1 ms (E), absence of LGE (F), reduced native T1 682 ms (G) and impaired 4-chamber LV-GLS –15% (H, associated Movie 2). Patient with mild dilated LV (I: diastole, J: systole) and mild LVEF dysfunction 53% (K, associated Movie 3), reduced myocardial T2* 17 ms (L) and hepatic T2* 11 ms (M), absence of LGE (N), reduced native T1 899ms (O) and 2-chamber impaired LV-GLS –16.6% (P, associated Movie 4). Patient with mild dilated LV (Q: diastole, R: systole) and normal LVEF 61% (S, associated Movie 5), normal myocardial T2* 33 ms (T), reduced hepatic T2* 6 ms (U), absence of LGE (V), normal native T1 944 ms (W) and impaired 2-chamber LV-GLS –18.6% (X, associated Movie 6).
cMR: cardiac magnetic resonance, LGE: late gadolinium enhancement, LVEF: left ventricular ejection fraction, LV-GLS: left ventricular global longitudinal strain, SSFP: steady-state free precession.

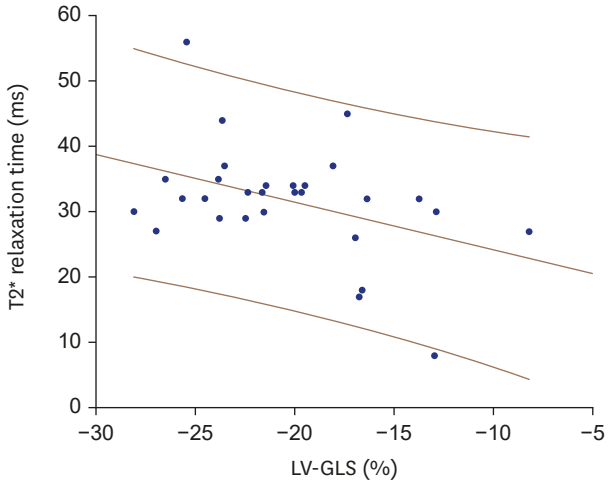

Figure 3. Correlation between myocardial T2* and LV GLS-feature tracking.
LV-GLS: left ventricular global longitudinal strain.

(MDS related cytopenia: 2 infections, 1 intracranial hemorrhage and 1 mesenteric ischemia) and the other because an unknown cause. Ten patients (32%) presented cardiovascular events: HF 16.1%, 1 HF with mid-range ejection fraction (HFmrEF) and 4 HF with preserved ejection fraction (HFpEF), and.6.5% required admission; pacemaker implantation due to atrioventricular block 3.2%, ischemic heart disease angina type 3.2%, and atrial fibrillation 6.5%. Three patients (9.7%) suffered both cardiovascular event and later death.

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Patients who suffered the combined event in the follow-up showed higher values (more pathological) of LV-GLS by MR-FT (–17.7 ± 5.5 vs. –21.7 ± 4.2, p = 0.047). However, we found no differences in the combined event occurrence according to the LV-GCS (–19.1 ± 8.8 vs. –21.6 ± 6.2, p = 0.46), LV-GRS (76.2 ± 29.4 vs. 87.4 ± 29.8, p = 0.36), or RV-GLS (–26.7 ± 5 vs. –28.8 ± 4, p = 0,359) values.

The ROC analysis revealed that a LV-GLS cut-off value of –17.7% had a sensitivity of 63% and a specificity of 81% for predicting the combined all-cause death and/or cardiovascular event (area under the curve = 0.69; 95% confidence interval [CI], 0.47–0.91) (**Figure 4**). Establishing the –17.7% LV-GLS cut-off, those patients who showed a LV-GLS value higher or equal to –17.7% suffered more frequently the combined cardiovascular event and all-cause mortality (LV-GLS ≥ –17.7 vs. LV-GLS < –17.7, 56% vs. 16%; log-rank 4.34; p = 0.037) (**Figure 5**). Time to event was significantly shorter in patients with pathological LV-GLS (LV-GLS ≥ –17.7: 483 days; 95% CI, 292–674 vs. LV-GLS < –17.7: 703 days; 95% CI, 605–802).

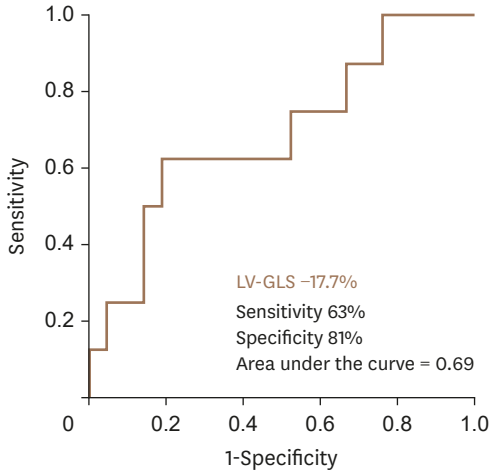

Figure 4. Receiver operating curve of LV-GLS by feature tracking for predicting all-cause death and/or cardiovascular event.
LV-GLS: left ventricular global longitudinal strain.

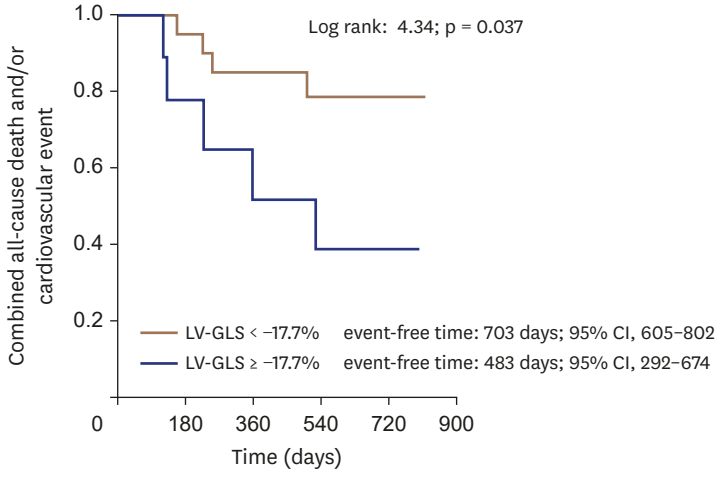

Figure 5. Kaplan Meier survival curve of LV-GLS by feature tracking for the combined all-cause death and/or cardiovascular event. Patients are stratified by LV-GLS ≥ –17.7% and < –17.7%. Individuals with LV-GLS ≥ –17.7% by magnetic resonance feature tracking suffered the combined event more frequently with a shorter event-free time.
GLS: global longitudinal strain, LV-GLS: left ventricular global longitudinal strain.

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After adjusting for age, sex, cardiovascular risk factors (arterial hypertension, diabetes mellitus, and dyslipidemia), LV volumes, mass and ejection fraction, myocardial T2* times, and NT-proBNP values, a higher LV-GLS value by FT remained as a predictor of the combined event in transfusion-dependent low-risk MDS patients (hazard ratio, 0.4; CI, 0.15–0.98; p = 0.045). Together with the LV-GLS, a T2* < 20 ms value and a higher value of NT-proBNP highlighted as independent predictors of the combined event.

DISCUSSION

The present study highlights the usefulness of myocardial deformation analysis by MR-FT in transfusion-dependent low-risk MDS patients.

IOC has been widely studied in the setting of hereditary anemias that require an intense transfusion support, mainly thalassemia major (TM). In MDS, this complication started to gain relevance in the last few years,[1] with the assumption of similar evolution than in other patients under chronic transfusions and few studies focused in MDS patients. Nevertheless, findings regarding diagnosis, treatment and prognosis cannot always be extrapolated from the TM population and it is necessary to perform this subset of analysis in order to clearly establish the potential cardiac damage in MDS population, generally older and with comorbidities that could modulate the iron damage and functional impact.

It is widely accepted that the diagnosis of MIO is made through T2* relaxation time, a technique well calibrated according to histological findings,[19] reproducible, accurate, and with prognostic value.[20] The presence of systolic dysfunction and HF are related to worse prognosis[6] and modifies the ICh strategy.[21] LVEF impairment is usually a late event, related to HF development, which is the most frequent cause of death in patients with IOC. Therefore, it is interesting to explore different imaging techniques that allow the early MIO and systolic dysfunction diagnosis.

Observational studies in TM patients have explored the myocardial deformation role in this field.[11][12][22-24] The strain quantified tissue Doppler imaging (TDI), 2- or 3-dimensional speckle tracking by echocardiography allows early detection of systolic dysfunction and is related to T2*. In thalassemia patients, myocardial deformation analysis by MR has been only performed using the tagging technique.[23] Myocardial deformation analysis by MR-FT in hematological malignancies requiring chronic transfusions had not been reported until now.

This study reveals the usefulness of MR-FT myocardial deformation analysis in MDS patients. Although the percentage of pathological LV-GLS was comparable by echocardiography and CMR in our population, CMR provides better image quality than echocardiography,[13] allowing its use in patients with poor acoustic window, in which the echocardiographic strain is usually not interpretable (29% of patients in our study). It does not require additional image acquisitions and involves fast post-processing, and its excellent reproducibility[13] makes it a perfect tool for the periodic monitoring of patients at risk or confirmed IOC. On the other hand, echocardiography as a single technique would not be useful for MIO diagnosis, so adding myocardial deformation to basal CMR, being the gold standard diagnostic technique, could be more useful.

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Our findings of impaired strain in MDS agree with those reported previously regarding its correlation with iron overload in TM patients.[12)24)] In addition, it once again shows its relationship with morphological and functional parameters related to HF such us LV dimensions, LVEF or NT-proBNP value.

The involvement of the different myocardial deformation parameters has not been consistent in the different studies in thalassemia. While some highlight the greater utility of circumferential strain,[12)] others show earlier involvement of longitudinal one,[24)25)] or the usefulness of strain rate[26)]; but its greater affectation with respect to the control group and its relationship with T2* remains constant in all studies.

GCS seems the most reproducible parameter in MR-FT among the different software,[18)] and it has been postulated that it could be the most affected parameter in IOC because the iron deposit starts in the subepicardial zone, whose fibers together with the means ones determine the circumferential contraction. However, although circumferential deformation was the most affected in our population, it was not significantly related to the occurrence of adverse events. On the other hand, LV-GLS measure is the largest and most robust prognostic parameter from echocardiography. Its prognostic value includes the MR-FT technique, despite not being frequently used at present.[27)28)] This study confirms its prognostic value in IOC environment in terms of cardiovascular events and mortality. Likewise, LV-GLS was the only parameter that correlated with myocardial T2*, with important prognostic value in population under transfusion support.[22)]

It has even been suggested that TDI and 2DSTI can be used for screening myocardial dysfunction and monitoring ICh therapy in β-TM patients.[12)] The morphological and functional heart affection in our study patients is more frequent than the MIO, so other causes of heart disease (ischemic, valve disease, chronic anemia…) may be involved. Therefore, it must be taken into account that the deterioration of myocardial strain and its prognostic value will not always be related to iron overload in this population. In MDS population, who is older and has a higher prevalence of other heart diseases different than IOC, the strain affectation may not always be useful for detecting and monitoring MIO. Therefore, the detection of pathological strain in these patients should lead to a cardiac study that determines the underlying cause of heart disease.

These findings may have significant implications for management decisions based on risk stratification of these patients, providing another tool to guide the specific treatment. MR multi-parametric approach has been proposed to provide prognostic information beyond MIO quantification in thalassemia patients.[29)] LV-GLS by MR-FT could be added to the grade of MIO by T2*, presence of fibrosis or the LVEF to improve cardiac outcomes. The strain impairment in patients with MIO probably requires the optimization of drugs with proven efficacy in HF addiction (*i.e.*, beta-blockers, angiotensin-converting enzyme inhibitors), and it is probably reasonable to initiate and/or optimize ICh therapy in suspected MIO cases. Subclinical detection of systolic dysfunction could allow for treatment adjustment before moving to more advanced stages with worse prognosis of IOC.

Regarding the study limitations, this is a single-center observational study, with a small number of patients and a short long-term follow-up, but similar to other series studied by cMR in this pathology. Although the MR-FT analysis was performed by a single observer, the reproducibility of this technique is excellent when carried out by an expert operator as in

the present study.[30] Other causes of heart disease different than IOC probably influence in strain parameters, although myocardial deformation impairment probably has prognostic value regardless of the heart disease cause. On the other hand, the reported sensitivity and specificity of LV-GLS to adverse events was not optimal. It is necessary to validate these results in a larger number of MDS patients, as well as other hematological diseases that require chronic transfusions. Furthermore, it would be necessary to establish whether the FT strain affectation should determine the start or optimization of ICh therapy.

In conclusion, MR-FT is a feasible technique, with good reproducibility and little increase in postprocessing time, which makes it possible to perform for MIO assessment. The longitudinal myocardial strain by cardiac magnetic resonance feature tracking in patients with low risk myelodysplastic syndromes is associated to myocardial iron overload, identifies patients with incipient systolic dysfunction and shows a prognostic value for the appearance of cardiovascular events and/or death.

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SUPPLEMENTARY MATERIAL

Supplementary Data 1
Material and methods

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REFERENCES

1. Remacha ÁF, Arrizabalaga B, Villegas A, et al. Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications. *Ann Hematol* 2015;94:779-87.
PUBMED | CROSSREF
2. Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. *J Clin Oncol* 2010;28:2847-52.
PUBMED | CROSSREF
3. Lyons RM, Marek BJ, Paley C, et al. Relation between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndromes: registry analysis at 5 years. *Leuk Res* 2017;56:88-95.
PUBMED | CROSSREF
4. Roy NB, Myerson S, Schuh AH, et al. Cardiac iron overload in transfusion-dependent patients with myelodysplastic syndromes. *Br J Haematol* 2011;154:521-4.
PUBMED | CROSSREF
5. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy: better understanding of an increasing disorder. *J Am Coll Cardiol* 2010;56:1001-12.
PUBMED | CROSSREF
6. Angelucci L, Li J, Greenberg PL, et al. Safety and efficacy, including event-free survival, of deferasirox versus placebo in iron-overloaded patients with low- and int-1-risk myelodysplastic syndromes (MDS): outcomes from the randomized, double-blind TELESTO study. *Blood* 2018;132:234.
CROSSREF
7. Du Y, Long Z, Chen M, Han B, Hou B, Feng F. Observational monitoring of patients with aplastic anemia and low/intermediate-1 risk of myelodysplastic syndromes complicated with iron overload. *Acta Haematol* 2017;138:119-28.
PUBMED | CROSSREF

8. Gu S, Xv Y, Fei C, et al. Labile plasma iron, more practical and more sensitive to iron overload in myelodysplastic syndromes. *Hematology* 2017;22:9-15.
PUBMED | CROSSREF
9. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;22:2171-9.
PUBMED | CROSSREF
10. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007;20:234-43.
PUBMED | CROSSREF
11. Di Odoardo LA, Giuditta M, Cassinerio E, et al. Myocardial deformation in iron overload cardiomyopathy: speckle tracking imaging in a beta-thalassemia major population. *Intern Emerg Med* 2017;12:799-809.
PUBMED | CROSSREF
12. Ari ME, Ekici F, Çetin İİ, et al. Assessment of left ventricular functions and myocardial iron load with tissue Doppler and speckle tracking echocardiography and T2* MRI in patients with β-thalassemia major. *Echocardiography* 2017;34:383-9.
PUBMED | CROSSREF
13. Maceira AM, Tuset-Sanchis L, López-Garrido M, et al. Feasibility and reproducibility of feature-tracking-based strain and strain rate measures of the left ventricle in different diseases and genders. *J Magn Reson Imaging* 2018;47:1415-25.
PUBMED | CROSSREF
14. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012;120:2454-65.
PUBMED | CROSSREF
15. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson* 2013;15:35.
PUBMED | CROSSREF
16. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, et al. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson* 2015;17:29.
PUBMED | CROSSREF
17. Almutairi HM, Boubertakh R, Miquel ME, Petersen SE. Myocardial deformation assessment using cardiovascular magnetic resonance-feature tracking technique. *Br J Radiol* 2017;90:20170072.
PUBMED | CROSSREF
18. Vo HQ, Marwick TH, Negishi K. MRI-derived myocardial strain measures in normal subjects. *JACC Cardiovasc Imaging* 2018;11:196-205.
PUBMED | CROSSREF
19. Carpenter JP, He T, Kirk P, et al. On T2* magnetic resonance and cardiac iron. *Circulation* 2011;123:1519-28.
PUBMED | CROSSREF
20. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;10:42.
PUBMED | CROSSREF
21. Wongjaikam S, Kumfu S, Chattipakorn SC, Fucharoen S, Chattipakorn N. Current and future treatment strategies for iron overload cardiomyopathy. *Eur J Pharmacol* 2015;765:86-93.
PUBMED | CROSSREF
22. Li SJ, Hwang YY, Ha SY, et al. Role of Three-dimensional speckle tracking echocardiography in the quantification of myocardial iron overload in patients with beta-thalassemia major. *Echocardiography* 2016;33:1361-7.
PUBMED | CROSSREF
23. Seldrum S, Pierard S, Moniotte S, et al. Iron overload in polytransfused patients without heart failure is associated with subclinical alterations of systolic left ventricular function using cardiovascular magnetic resonance tagging. *J Cardiovasc Magn Reson* 2011;13:23.
PUBMED | CROSSREF
24. Pizzino F, Meloni A, Terrizzi A, et al. Detection of myocardial iron overload by two-dimensional speckle tracking in patients with beta-thalassaemia major: a combined echocardiographic and T2* segmental CMR study. *Int J Cardiovasc Imaging* 2018;34:263-71.
PUBMED | CROSSREF
25. Parsaee M, Saedi S, Joghataei P, Azarkeivan A, Alizadeh Sani Z. Value of speckle tracking echocardiography for detection of clinically silent left ventricular dysfunction in patients with β-thalassemia. *Hematology* 2017;22:554-8.
PUBMED | CROSSREF

26. Cheung YF, Liang XC, Chan GC, Wong SJ, Ha SY. Myocardial deformation in patients with beta-thalassemia major: a speckle tracking echocardiographic study. *Echocardiography* 2010;27:253-9.
PUBMED | CROSSREF

27. Eitel I, Stiermaier T, Lange T, et al. Cardiac magnetic resonance myocardial feature tracking for optimized prediction of cardiovascular events following myocardial infarction. *JACC Cardiovasc Imaging* 2018;11:1433-44.
PUBMED | CROSSREF

28. Romano S, Judd RM, Kim RJ, et al. Feature-tracking global longitudinal strain predicts death in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy incremental to ejection fraction and late gadolinium enhancement. *JACC Cardiovasc Imaging* 2018;11:1419-29.
PUBMED | CROSSREF

29. Pepe A, Meloni A, Rossi G, et al. Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. *Eur Heart J Cardiovasc Imaging* 2018;19:299-309.
PUBMED | CROSSREF

30. Feisst A, Kuetting DL, Dabir D, et al. Influence of observer experience on cardiac magnetic resonance strain measurements using feature tracking and conventional tagging. *Int J Cardiol Heart Vasc* 2018;18:46-51.
PUBMED | CROSSREF