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ORIGINAL ARTICLE

Prognostic value of multiparametric cardiac magnetic resonance in sickle cell patients

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Abstract

The aim of this multicenter study was to prospectively assess the predictive value of multiparametric cardiac magnetic resonance (CMR) for cardiovascular complications in sickle cell disease (SCD) patients. Among all patients with hemoglobinopathies consecutively enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) Network, we selected 102 SCD patients (34.38 ± 12.67 years, 49 females). Myocardial iron overload (MIO) was measured by the multislice multiecho T2* technique. Atrial dimensions and biventricular function parameters were quantified by cine images. Late gadolinium enhancement (LGE) images were acquired to detect focal myocardial fibrosis. At baseline CMR, only two patients had significant MIO (global heart T2* < 20 ms). During a mean follow-up of 63.01 ± 24.95 months, 11 cardiovascular events (10.8%) were registered: 3 pulmonary hypertension, 2 supraventricular arrhythmias, 1 heart failure, 1 death for heart failure, 1 pulmonary embolism, 1 peripheral vascular disease, 1 transient ischemic attack, and 1 death after acute chest syndrome. In the multivariate analysis, the independent CMR predictors of cardiovascular events were left ventricular (LV) ejection fraction (hazard ratio-HR = 0.88; $p = 0.025$) and right ventricular (RV) mass index (HR = 1.09; $p = 0.047$). According to the receiver-operating characteristic curve analysis for adverse events, an LV ejection fraction < 58.9% and an RV mass index > 31 g/m^2 were optimal cut-off values. Reduced left ventricular ejection fraction and increased right ventricular mass index showed a significant prognostic value in patients with SCD. Our data seem to suggest that CMR may be added as a screening tool for identifying SCD patients at high risk for cardiopulmonary and vascular diseases.

Keywords Sickle cell disease · Cardiovascular complications · Magnetic resonance imaging · Prognosis

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Introduction

Sickle cell disease (SCD) is one of the most common inherited disorders of hemoglobin (Hb) production and has been recognized as a global public health problem. SCD is caused by mutations in the beta-globin gene that lead to the production of an abnormal Hb variant, known as HbS [1]. SCD can occur due to homozygosity for the HbS gene (HbSS), due to compound heterozygosity for HbS and another structural hemoglobin variant, such as hemoglobin C or D, and due to double heterozygosity of HbS and beta-thalassemia (HbS/β-thalassemia or sickle cell/β-thalassemia) [2]. HbS/β-thalassemia represents the most prevalent form of sickling syndromes in Italy due to the high frequency of the β-thalassemia trait.

Thanks to several advances in the diagnosis and treatment, including childhood vaccination, new-borns screening, penicillin prophylaxis for pneumococcal infection in childhood, red blood cell transfusion, hydroxyurea therapy, and comprehensive medical care, early childhood mortality of SCD patients has dramatically decreased in high-income countries. In the aging population, cardiovascular complications are emerging as a major cause of reduced quality of life and early mortality [3, 4].

The two clinical hallmarks of SCD, hemolysis and vaso-occlusive crises with repeated episodes of ischemia and reperfusion, strongly contribute to cardiovascular involvement [5, 6]. The microvascular dysfunction related to repeated vaso-occlusive events and the nitric oxide scavenging resulting from chronic intravascular haemolysis trigger a chronic inflammatory state and widespread vasculopathy, that can damage multiple organs, including the heart and the lungs [7, 8]. The chronic hemolysis-related anemia is associated with a compensatory increase in blood volume [9], which enhances the ventricular pump performance. The anatomical–functional expression of this chronic state is the dilatation of all cardiac chambers [10, 11]. Over time, progressive dilation leads to increased wall stress and eccentric hyperthrophy [12]. This volume overload state can lead to increased filling pressures, increased venous return, abnormal pulmonary hemodynamics, arrhythmias, and the syndrome of high-output heart failure [13]. Of note, it has been suggested that the high-output state of SCD, rather than primary abnormalities of the pulmonary microvasculature, represents the major driver of pulmonary hypertension (PH) [14].

Chronic transfusion therapy can reduce both hemolytic anemia and vaso-occlusive sickling episodes [15], but can add another potential factor of stress for the cardiovascular system: a secondary state of iron overload [16]. Cardiac and vascular iron overload may reduce ventricular dimensions initially through vascular and ventricular stiffening [17, 18] but may increase ventricular dimensions and decrease systolic function in end-stage disease [19, 20]. Myocardial iron overload (MIO) is relatively rare in patients with SCD [21–23], but the increasing life expectancy and duration of chronic transfusion will make MIO a more significant clinical problem.

Due to its multiparametric nature, cardiac magnetic resonance (CMR) represents a powerful tool to evaluate structural and functional impairments in the myocardium of SCD patients. T2* CMR is the method of choice for the non-invasive, fast, and reproducible quantification of MIO [24] and has been validated against histological findings [25, 26]. CMR is the gold standard for the non-invasive assessment of biventricular size and function with excellent accuracy and reproducibility [27]. In particular, CMR provides the most comprehensive information on the right ventricle, by virtue of its high spatial and temporal resolution, its excellent signal-to-noise ratio between the myocardium and the blood pool, and the fact that, conversely to echocardiography, it is free from acoustic window limitations and independent of geometric assumptions. Finally, following the injection of a contrast agent, CMR represents a valuable tool for the detection of myocardial fibrosis [28]. In SCD, many processes including anemia, ischemia, inflammation, and microvascular disease may predispose to myocardial fibrosis [29].

There are no prospective cohort studies evaluating the association between multiparametric CMR findings (heart iron, function, and fibrosis) and cardiovascular outcomes in SCD patients. Therefore, the aim of this multicenter study was to prospectively assess the predictive value of CMR parameters for cardiovascular complications in SCD patients.

Methods

Patients

Among all patients with hemoglobinopathies consecutively enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) Network, we selected only those with SCD ($N = 109$: 48% females, mean age 35.08 ± 12.87 years). Globally, the following inclusion criteria were adopted in the MIOT Network: (1) male and female patients, of all ages, with thalassemia syndromes or structural hemoglobin variants, requiring magnetic resonance imaging (MRI) to quantify cardiac and liver iron burden; (2) written informed consent; (3) written authorization for use and disclosure of protected health information; (4) no absolute contraindications to MRI.

The MIOT Network was a collaborative project among more than 60 hematological centers and 10 validated MRI sites, where MRI exams were performed using

homogeneous, standardized, and validated procedures [30, 31]. All centers were linked by a shared database [32], where the clinical-anamnestic history of the patients, from birth to the date of the first MRI scan, was recorded. All patients performed a routine screening and at every MRI follow-up, performed by protocol every 18 ± 3 months, the clinical, instrumental, and laboratory data were updated. Clinical follow-up continued until September 2016. Each hematologist completed a case report form detailing patient outcomes between the last MRI and September 2016.

The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients provided informed consent.

Magnetic resonance

All MRI examinations were performed with a clinical 1.5 T scanner (GE Healthcare, Milwaukee, WI, USA). An eight-element cardiac phased-array receiver surface coil with breath-holding in end-expiration and ECG-gating was used.

The T2* technique was used for iron overload assessment. A single mid-hepatic slice [33] and three parallel short-axis views (basal, medium, and apical) of the left ventricle (LV) were acquired in the same imaging session [30, 34]. T2* images analysis was performed using a custom-written, previously validated software (HIPPOMIOT®) [35]. Hepatic T2* values were calculated in a circular region of interest [36] and were converted into liver iron concentration (LIC) using Wood's calibration curve [37, 38]. The software provided the T2* value for all 16 segments of the LV, according to the standard American Heart Association (AHA)/American College of Cardiology (ACC) model [39], and the global heart T2* value was obtained by averaging all segmental values.

For the quantification of biventricular function parameters, cine images were acquired in sequential 8 mm short-axis slices (gap 0 mm) from the atrioventricular ring to the apex. Images were analyzed in a standard way using MASS® software (Medis, Leiden, The Netherlands) [40]. Atrial areas were measured from the 4-chamber view projection in the ventricular end-systolic phase. Biventricular volumes and masses and bi-atrial areas were normalized for the body surface area.

To detect the presence of focal/macroscopic myocardial fibrosis, late gadolinium enhancement (LGE) short-axis and vertical, horizontal, and oblique long-axis images were acquired 10–18 min after Gadobutrol (Gadovist®; Bayer Schering Pharma; Berlin, Germany) intravenous administration at the standard dose of 0.2 mmol/kg. LGE images were not acquired in patients with a glomerular filtration rate < 30 mL/min/1.73m^2 and in patients who refused. LGE was considered present when visualized in two different views [41, 42].

Diagnostic criteria

An MR LIC ≥ 3 mg/g/dw was considered indicative of significant iron load [43]. A T2* measurement of 20 ms was taken as a "conservative" normal value for segmental and global values [20].

The outcome of this study was the incidence of cardiovascular complications, defined as a composite of cardiac complications and pulmonary, cerebral, and peripheral vascular diseases. Heart failure (HF) was identified based on symptoms, signs, biomarkers, and instrumental parameters, according to the current guidelines [44]. Arrhythmias were diagnosed and classified according to the AHA/ACC Guidelines [45]. PH was diagnosed if the trans-tricuspidal velocity jet on trans-thoracic echocardiogram was > 3.2 m/s [46] in presence of signs and symptoms. In case of suspicion, the diagnosis of pulmonary embolism (PE) was accurately confirmed or ruled out by non-invasive imaging tests [47]. The diagnosis of a transient ischemic attack (TIA) was made based on symptoms, objective findings on neurologic examination, and imaging of the brain [48]. The clinical diagnosis of deep vein thrombosis was confirmed by objective testing using ultrasound or venography. If a patient developed more than one complication, only the first one was considered.

Statistical analysis

All data were analyzed 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). Categorical variables were expressed as frequencies and percentages.

The normality of the distribution of the continuous variables was assessed by using the Kolmogorov–Smirnov test.

Comparisons between two groups were made by independent-samples *t*-test for continuous variables with normal distribution and Mann–Whitney *U* test for continuous variables with non-normal distribution. $\chi 2$ testing was performed for categorical variables.

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

The Cox proportional-hazard model was used to test the association between the considered prognostic variables and the outcome. The variables with a statistical significance in the univariable analysis were placed in the multivariate model. They were ruled out if they did not significantly improve the adjustment of the model. The results were presented as hazard ratio (HR) with 95% confidence intervals (CI).

The optimal cut-off value of clinical variables with statistical significance in the multivariable analysis was assessed

using a receiver-operating characteristic (ROC) curve analysis for the endpoint of this study.

A $P < 0.05$ was considered statistically significant.

Results

Baseline data

Seven patients were excluded from this study because a cardiac complication (4 arrhythmias, 2 HF, and 1 PH) was present at the baseline MRI.

The baseline demographic, clinical, and MRI features of the 102 considered SCD patients are described in Table 1. Patients were homogeneously distributed in terms of gender and the mean age was 34.38 ± 12.67 years. Forty-nine (48.0%) patients were under regular transfusion regimen (≥ 4 transfusions/year): 39 received simple transfusions (mean number of transfusions/year 11.78 ± 6.62) and 10 exchange transfusions (mean number of transfusions/year 10.50 ± 3.93). No significant difference in serum hemoglobin levels was detected between never/sporadically transfused patients and regularly transfused patients (9.44 ± 1.25 g/dl vs 9.42 ± 1.24 g/dl; $P = 0.881$). Hemoglobin levels were not associated with biventricular volume or mass indexes but showed a weak positive correlation with LV ejection fraction (EF) ($R = 0.232$; $P = 0.029$). Half of SCD patients were on no iron chelation therapy. Among the 51 chelated patients, 27 were receiving deferoxamine, 15 deferasirox, 7 deferiprone, and 2 deferoxamine in combination with deferiprone. Hepatic and myocardial iron overload were detected, respectively, in the 54.9% (56/102) and 2.0% (2/102) of patients. The contrast medium was administrated only in 66 patients, of whom 10 (15.2%) had nonischemic focal myocardial fibrosis. A mesocardial LGE at the insertion points of the free RV wall in the interventricular septum was found in 5 patients.

Twenty-four patients had homozygous HbSS and 78 patients had HbS/β-thalassemia. The latter group included both HbS/β0 thalassemia and HbS/β + thalassemia patients, not further differentiated according to the beta-globin mutation. The comparison between HbSS and HbS/β-thalassemia groups is shown in Table 1. Surgical splenectomy and treatment with hydroxyurea were significantly less common in HBSS than in HbS/β-thalassemia patients, but HBSS patients were more frequently regularly transfused. Hepatic and cardiac iron overload, biventricular function parameters, and bi-atrial areas were comparable between the two groups.

Table 1 Baseline demographic, clinical and MRI findings in SCD patients divided into two groups based on the SCD genotype

Variable	All patients ($N = 102$)	Homozygous HbS ($N = 24$)	Hbs/β-thalassemia ($N = 78$)	*P*
Females, N (%)	49 (48.0)	10 (41.7)	39 (50.0)	0.475
Age (years)	34.38 ± 12.67	30.84 ± 12.49	35.47 ± 12.61	0.117
Splenectomy, N (%)	58 (56.9)	7 (29.2)	51 (65.4)	0.002
Regularly transfusions, N (%)	49 (48.0)	17 (70.8)	32 (41.0)	0.011
Chelation therapy, N (%)	51 (50.0)	12 (50.0)	39 (50.0)	1.000
Hydroxyurea therapy, N (%)	48/85 (56.5)	8/21 (38.1)	40/64 (62.5)	0.050
Serum hemoglobin (g/dl)	9.43 ± 1.24	9.72 ± 1.40	9.35 ± 1.19	0.267
Serum ferritin (ng/l)	1308.99 ± 1528.83	1714.42 ± 1824.36	1200.49 ± 1435.04	0.308
MRI LIC (mg/g/dw)	6.82 ± 9.89	9.22 ± 16.79	6.08 ± 6.45	0.862
MRI LIC ≥ 3 mg/g/dw, N (%)	56 (54.9)	13 (54.2)	43 (55.1)	0.934
Global heart T2(ms)*	35.99 ± 6.42	37.99 ± 5.12	35.37 ± 6.68	0.080
Global heart T2 < 20 ms, N (%)*	2 (2.0)	0 (0.0)	2 (2.6)	1.000
N. of segments with T2 < 20 ms*	1.06 ± 2.37	0.46 ± 1.14	1.24 ± 2.61	0.069
LV EDVI (ml/m^2)	93.71 ± 20.73	94.35 ± 22.39	93.51 ± 20.33	0.806
LV mass index (g/m^2)	62.17 ± 16.95	63.24 ± 21.89	61.83 ± 15.23	0.859
LV EF (%)	61.39 ± 6.86	63.35 ± 5.82	60.78 ± 7.07	0.109
RV EDVI (ml/m^2)	84.17 ± 20.51	83.92 ± 20.92	84.25 ± 20.52	0.732
RV mass index (g/m^2)	30.31 ± 8.98	34.58 ± 11.45	29.91 ± 7.63	0.070
RV EF (%)	63.13 ± 7.82	63.42 ± 8.18	63.04 ± 7.76	0.839
Focal myocardial fibrosis, N(%)	10/66 (15.2)	3/15 (20.0)	7/51 (13.7)	0.683
Left atrial area (cm^2/m^2)	12.77 ± 2.61	13.62 ± 3.16	12.41 ± 2.28	0.089
Right atrial area (cm^2/m^2)	11.89 ± 2.26	11.69 ± 2.38	11.99 ± 2.22	0.640

N, number; *MRI*, magnetic resonance imaging; *LIC*, liver iron concentration; *LV*, left ventricular; *EDVI*, end-diastolic volume index; *EF*, ejection fraction; *RV*, right ventricular

Prediction of cardiovascular complications

The mean follow-up time was 63.01 ± 24.95 months (median = 64.71 months). Cardiovascular events were recorded in 11 (10.8%) patients: 3 pulmonary hypertension, 2 supraventricular arrhythmias, 1 heart failure, 1 death for heart failure, 1 pulmonary embolism, 1 peripheral vascular disease, 1 transient ischemic attack, and 1 death after acute chest syndrome. The mean age at the first complication was 45.86 ± 10.21 years (range: 29–57 years). The mean time from the first MRI to the development of a cardiac complication was 50.77 ± 26.72 months.

Table 2 shows the comparison of baseline characteristics as well as MRI parameters between patients free of events and patients who developed a cardiovascular event. No significant difference was detected for gender, type of SCD (HbS homozygosity vs compound heterozygosity for HbS and either β0 or β + thalassemia), presence of regular transfusions or chelation therapy, and indices of iron overload. Cardiovascular events were associated with aging and with lower baseline serum hemoglobin levels. Patients suffering a cardiovascular event had significantly lower LV EF and significantly higher right ventricular (RV) mass index at the baseline MRI while no difference was found in all other biventricular function parameters or atrial areas.

Table 3 shows the results of the univariate Cox regression analysis. Among the non-MRI parameters, aging and lower serum hemoglobin levels emerged as the significant univariate prognosticators of cardiovascular complications. Multivariate analysis revealed that both variables remained prognostic indicators (age: HR = 1.08, 95%CI = 1.01–1.15, $P = 0.025$ and serum hemoglobin: HR = 0.33, 95%CI = 0.14–0.76, $P = 0.010$). No significant correlation was detected between age and serum hemoglobin levels ($R = -0.064$, $P = 0.551$). Among the MRI parameters, LV EF and RV mass index were significant univariate prognosticators of cardiovascular complications. Both variables remained significant prognosticators at the multivariate analysis (LV EF: HR = 0.88, 95%CI = 0.79–0.98, $P = 0.025$ and RV mass index: HR = 1.09, 95%CI = 1.01–1.18, $P = 0.047$). Due to the low number of events, it was not possible to perform a multivariate model including all four univariate prognosticators.

The patient who died of HF showed a baseline global heart T2* = 9.94 ms and all segments with T2* < 20 ms.

Table 2 Comparison of baseline characteristics in SCD patients free of events versus those who developed a cardiovascular event during the follow-up

Variable	No cardiovascular events ($N = 91$)	Cardiovascular events ($N = 11$)	P
Females, N (%)	47 (51.6)	6 (54.5)	0.856
Age (yrs)	33.51 ± 12.69	41.63 ± 10.37	0.044
Type of SCD, N (%)			
Homozigous HbS	23 (25.3)	1 (9.1)	0.451
HbS/β-thalassemia	68 (74.7)	10 (90.9)	
Splenectomy, N (%)	51 (56.0)	7 (63.6)	0.753
Regular transfusions, N (%)	44 (48.4)	5 (45.5)	0.856
Chelation therapy, N (%)	44 (48.4)	7 (63.9)	0.525
Hydroxyurea therapy, N (%)	41/75 (54.7)	7/10 (70.0)	0.502
Serum hemoglobin (g/dl)	9.56 ± 1.20	8.41 ± 1.07	0.001
Serum ferritin (ng/l)	1323.62 ± 1564.33	1191.90 ± 1271.25	0.653
MRI LIC (mg/g/dw)	6.83 ± 10.19	6.72 ± 7.28	0.750
MRI LIC ≥ 3 mg/g/dw, N (%)	49 (53.8)	7 (63.6)	0.750
Global heart T2(ms)*	36.11 ± 5.90	35.00 ± 10.11	0.817
Global heart T2 < 20 ms, N (%)*	1 (1.1)	9 (9.1)	0.205
N. of segments with T2 < 20 ms*	0.95 ± 1.91	2.00 ± 4.79	0.955
LV EDVI (ml/m^2)	93.36 ± 20.76	96.53 ± 21.28	0.559
LV mass index (g/m^2)	61.54 ± 16.83	67.25 ± 17.89	0.268
LV EF (%)	62.01 ± 6.72	56.47 ± 6.13	0.011
RV EDVI (ml/m^2)	83.99 ± 20.58	85.65 ± 20.85	0.804
RV mass index (g/m^2)	29.71 ± 9.22	34.87 ± 5.23	0.031
RV EF (%)	63.50 ± 7.55	60.13 ± 9.67	0.179
Focal myocardial fibrosis, N (%)	10/59 (16.9)	0/7 (0.0)	0.583
Left atrial area (cm^2/m^2)	12.84 ± 2.65	12.13 ± 2.27	0.500
Right atrial area (cm^2/m^2)	11.85 ± 2.31	12.29 ± 1.89	0.627

N, number; *SCD*, sickle cell disease; *MRI*, magnetic resonance imaging; *LIC*, liver iron concentration; *LV*, left ventricular; *EDVI*, end-diastolic volume index; *EF*, ejection fraction; *RV*, right ventricular

Table 3 Results of univariate and multivariate Cox regression analysis

	Univariate analysis	
	HR (95%CI)	*P*
Male gender	0.95 (0.29–3.15)	0.933
Age	1.07 (1.01–1.13)	0.034
Homozigous HBS mutation	0.29 (0.04–2.27)	0.237
Splenectomy	1.20 (0.35–4.13)	0.768
Regularly transfusions	0.78 (0.23–2.62)	0.686
Chelation therapy	1.66 (0.49–5.71)	0.418
Hydroxyurea therapy	1.42 (0.36–5.62)	0.615
Serum hemoglobin	0.034 (0.16–0.74)	0.006
Serum ferritin	1.00 (1.00–1.00)	0.780
MRI LIC	1.00 (0.95–1.06)	0.941
*Global heart T2**	0.98 (0.89–1.07)	0.631
N. of segments with T2 < 20 ms*	1.12 (0.94–1.34)	0.188
LV EDVI	1.01 (0.98–1.03)	0.827
LV mass index	1.02 (0.98–1.05)	0.402
LV EF	0.88 (0.80–0.97)	0.007
RV EDVI	1.00 (0.98–1.03)	0.876
RV mass index	1.07 (1.01–1.14)	0.046
RV EF	0.94 (0.87–1.03)	0.175
Focal myocardial fibrosis	0.04 (0.00–48.10)	0.501
Left atrial area index	0.88 (0.66–1.18)	0.384
Right atrial area index	1.01 (0.74–1.39)	0.936

N, number; *SCD*, sickle cell disease; *MRI*, magnetic resonance imaging; *LIC*, liver iron concentration; *LV*, left ventricular; *EDVI*, end-diastolic volume index; *EF*, ejection fraction; *RV*, right ventricular

The patient who developed HF had a baseline global heart T2* = 24.94 ms but 4 segments with T2* < 20 ms. The other patient with a baseline global heart T2* < 20 ms did not develop a cardiovascular complication during the follow-up but after the MRI she changed the chelation regimen, switching from deferoxamine in monotherapy to sequential deferoxamine/deferiprone.

Optimal cut-off values of CMR predictors for cardiovascular complications

At ROC curve analysis, an LV EF < 58.9% predicted the presence of future cardiovascular events with a sensitivity of 72.7 and a specificity of 71.9 ($P = 0.002$). The area under the curve was 0.71 (95%CI: 0.63–0.81) (Fig. 1A).

A RV mass index > 31 g/m^2 predicted the presence of future cardiovascular events with a sensitivity of 87.5% and a specificity of 62.3% ($P = 0.001$). The area under the curve was 0.74 (95%CI: 0.62–0.84) (Fig. 1B).

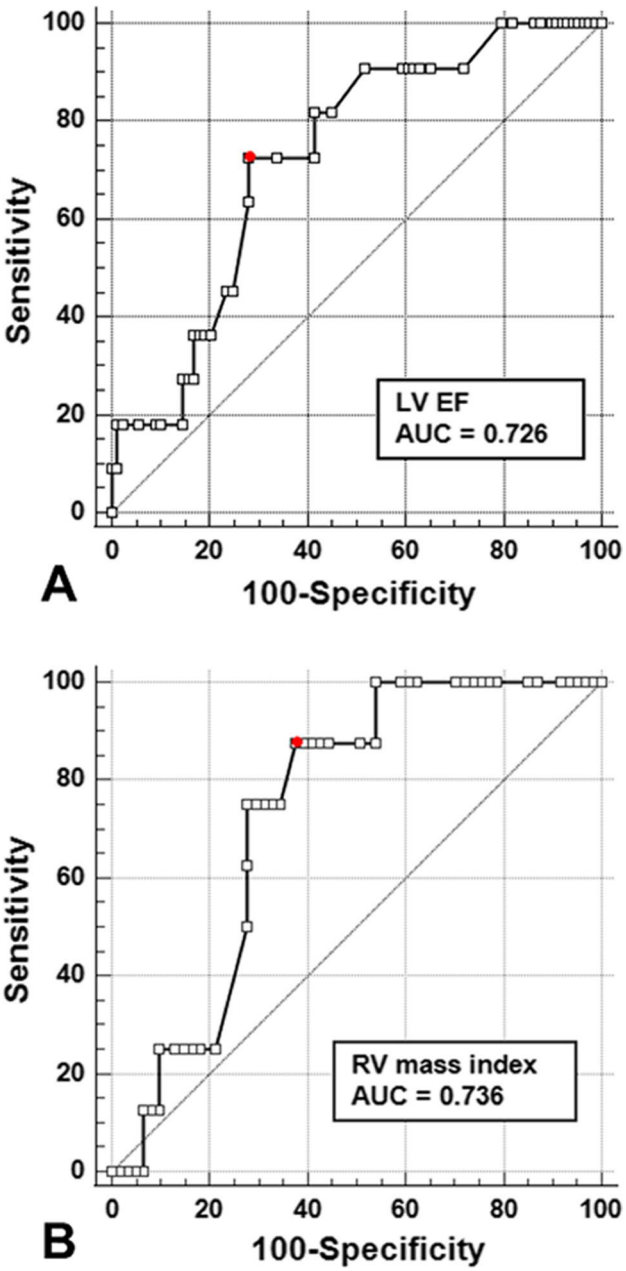

Fig. 1 ROC curve analysis of left ventricular ejection fraction (**A**) and RV mass index (**B**) to predict cardiovascular events

Discussion

To the best of our knowledge, this is the first study exploring the value of multiparametric CMR, including RV mass assessment, in the prognostic evaluation of SCD patients.

We included patients with homozygous HbS and HbS/β-thalassemia. HbS/β-thalassemias are classified as HbS/β0 thalassemia and HbS/β + thalassemia, with the former being characterized by the absence of adult hemoglobin and a severe clinical course similar to homozygous SCD [49]. HbS/β + thalassemia is clinically heterogeneous, with variable residual amounts of adult hemoglobin that determine the clinical course [50]. A recent echocardiographic study showed that diameters, thicknesses, masses, and volumes of cardiac chambers were comparable between HbS/β0 thalassemia and HbS/β + thalassemia patients, suggesting that, unlike other clinical parameters, the cardiac involvement in this disease does not depend so much on the thalassemia genotype [51]. In the present study, we detected comparable cardiac T2* values and biventricular function parameters by CMR between homozygous HbS and HbS/β-thalassemia patients and we considered all patients as a unique group, irrespective of the genotype.

In our cohort of SCD patients, reduced LV EF and increased RV mass index emerged as CMR-independent predictors of cardiovascular complications. LV EF is the most commonly used surrogate marker of LV systolic function. A meta-analysis including 19 studies reported no significant differences between SCD patients and controls in LV EF assessed by echocardiography [52]. Unlike diastolic dysfunction, systolic dysfunction is considered rare among SCD patients [53]. Indeed, according to our ROC analysis, a relatively high threshold for LV EF (< 58.9%) predicted the presence of future cardiovascular events. In our cohort, LV EF was significantly correlated with hemoglobin, suggesting that chronic anemia plays a key role in depressing LV systolic function and, consequently, in the development of cardiovascular complications. In support of this thesis, serum hemoglobin emerged as a clinical univariate prognosticator of cardiovascular complications. However, the microcirculation damage due to vaso-occlusive crisis has been demonstrated to be another important contributor to the deterioration of LV systolic function [54]. In SCD, abnormal myocardial perfusion and flow reserve, related to erythrocyte sickling that occludes the small arteries, capillaries, and venules and endothelial proliferation, have been demonstrated by echocardiography [54] and myocardial scintigraphy [55, 56]. In a study involving 22 children with SCD, myocardial perfusion defects were found in 8 patients, of whom 5 had cardiac symptoms (three episodes of cardiac failure, one of ventricular fibrillation, and one angina) [56].

Traditionally, the importance of the RV has been underestimated and overlooked in clinical practice and literature. However, in the last decades, the central role of the RV in the management and prognosis of many cardiac diseases has been recognized, changing our perspective towards the right side of the heart [57]. Junqueira et al. showed that SCD patients had significantly higher RV mass index than healthy subjects [58]. Pulmonary vascular endothelial damage/dysfunction can result in the loss of vascular reactivity, and activation of proliferative and antiapoptotic pathways, leading to vascular remodeling, and elevated pulmonary artery pressure [59]. Moreover, the high cardiac output causes increased pulmonary pressure regardless of whether pulmonary vascular resistance is high or not [60]. As pulmonary pressures increase, the thin-walled RV begins to hypertrophy and based on our results, an RV mass index of $31 > g/m^2$ can predict the development of cardiovascular events. So, although larger studies are needed to confirm the prognostic impact of an increased RV mass index, the RV mass assessment should be included in the routine MRI of SCD patients. Since all three patients who developed PH had an RV mass index > 31 g/m^2, the combination of both Doppler echocardiography, which represents the non-invasive screening test for PH [61], and MRI may increase the positive predictive value [62] for the detection of right heart catheterization (RHC)–confirmed PH. Although trans-thoracic echocardiography is largely used as an initial imaging modality, it has limited diagnostic capabilities for the evaluation of RV due to its thin wall, peculiar morphology, and the anterior position in the chest.

In contrast to thalassemia major patients [63, 64], we did not detect an association between MIO and cardiac complications, most likely because significant MIO was detected only in two patients, and there were only two cases of heart failure. It has been demonstrated that MIO contributes less to the development of arrhythmias and pulmonary hypertension than cardiac failure [63–66]. However, it should be pointed out that one of the two patients with significant MIO died of HF and in the other patient, the abnormal T2* prompted changes in clinical management. Indeed, the early start of aggressive chelation therapy can prevent, delay, or even reverse iron cardiomyopathy [67]. Although SCD patients have a lower risk for developing myocardial siderosis as compared to other hemoglobinopathies [68], our findings suggest once cardiac iron is present, it is associated with its own toxicity.

The contrast medium was administrated only in 66% of patients, partially explaining the absence of a correlation between focal fibrosis and cardiovascular complications. Most importantly, the LGE technique relies on the contrast between normal and abnormal myocardium areas and cannot accurately detect a more diffuse fibrotic process affecting the whole myocardium [69]. Conversely to focal fibrosis [58], diffuse myocardial fibrosis was found to be a common process in both mice models [70] and patients with SCD [71], associated with diastolic dysfunction and the restrictive physiology features of SCD-related cardiomyopathy.

Beyond CMR, aging emerged as a significant predictor of cardiovascular complications. Aging itself results in

well-defined phenotypic changes, which render the cardiovascular system prone to disease, even in the absence of traditional and non-traditional risk factors [72]. On the other hand, as patients live longer, the chronic effects of sustained hemolytic anemia and vaso-occlusive events accumulate [53].

This study is limited by the low number of patients and of cardiovascular events, which prevented us to evaluate the prognostic association between the MRI parameters and the different types of cardiovascular events, considered separately. Larger studies are needed to explore this issue. Another limitation is that the diagnosis of PH was not confirmed by RHC. Although RHC is the diagnostic gold standard for PH [73], it is an invasive and expensive procedure, unsuitable as a screening tool. Moreover, we did not have sufficient information on the quantitative β-globin defect of HbS/β-thalassemia patients (β0 or β + mutation) and we did not assess at the baseline MRI the hemoglobin A percentage, which could have been useful to better characterize or stratify our population.

Conclusion

Reduced left ventricular ejection fraction and increased right ventricular mass index showed a significant prognostic value in patients with SCD. This finding suggests that multiparametric CMR may be added as a screening tool for identifying SCD patients at high risk for cardiopulmonary and vascular diseases.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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