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CLINICAL RESEARCH
Imaging

National networking in rare diseases and reduction of cardiac burden in thalassemia major

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Aims A tailored chelation therapy guided by magnetic resonance imaging (MRI) is a strategy to improve the prognosis in iron-loaded patients, in many cases still hampered by limited MRI availability. In order to address this issue, the Myocardial Iron Overload in Thalassemia (MIOT) network was established in Italy and we aimed to describe the impact of 10-year activity of this network on cardiac burden in thalassemia major (TM).

Methods and results Within the MIOT network, 1746 TM patients (911 females; mean age 31.2 ± 9.1 years) were consecutively enrolled and prospectively followed by 70 thalassemia and 10 MRI centres. Patients were scanned using a multiparametric approach for assessing myocardial iron overload (MIO), biventricular function, and myocardial fibrosis. At the last MRI scan, a significant increase in global heart T2* values and a significantly higher frequency of patients with no MIO (all segmental T2* ≥20 ms) were detected, with a concordant improvement in biventricular function, particularly in patients with baseline global heart T2* <20 ms. Forty-seven percentage of patients changed the chelation regimen based on MRI. The frequency of heart failure (HF) significantly decreased after baseline MRI from 3.5 to 0.8% ($P < 0.0001$). Forty-six patients died during the study, and HF accounted for 34.8% of deaths.

Conclusion Over 10 years, continuous monitoring of cardiac iron and a tailored chelation therapy allowed MIO reduction, with consequent improvement of cardiac function and reduction of cardiac complications and mortality from MIO-related HF. A national networking for rare diseases therefore proved effective in improving the care and reducing cardiac outcomes of TM patients.

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Key Question

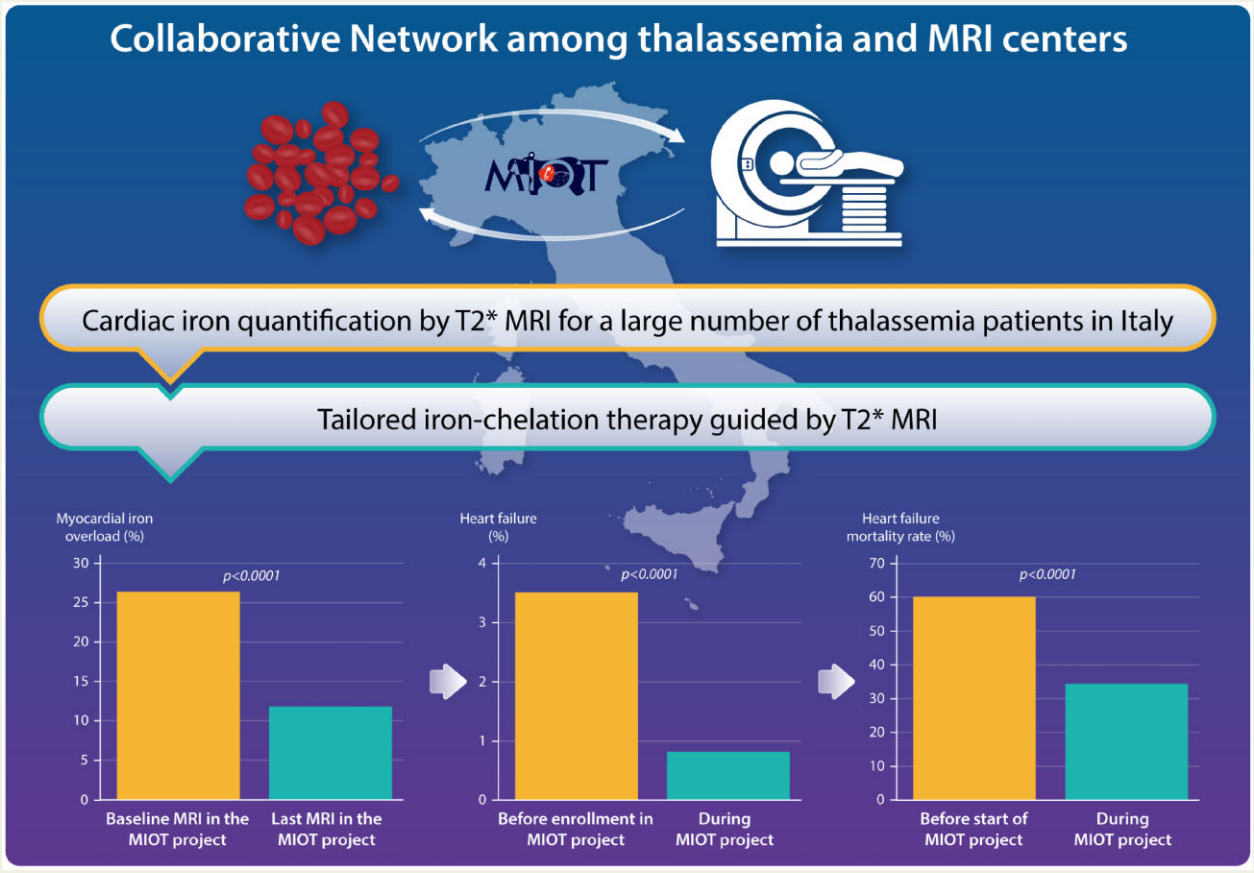
Which was the impact on cardiac outcomes in thalassemia major by a national network among thalassemia and magnetic resonance imaging centres ensuring the continuous and standardized monitoring of the cardiac iron levels?

Key Finding

There was a reduction of myocardial iron overload (MIO) in almost 70% of patients, with consequent improvement of cardiac function and reduction of cardiac complications and mortality from MIO-related heart failure.

Take Home Message

A national clinical and imaging networking in rare diseases was effective in improving the care and in reducing the cardiac burden in thalassemia major patients.



Structured Graphical Abstract A national clinical and imaging networking for the continuous and standardized monitoring of the cardiac iron levels was effective in improving the care and in reducing the cardiac complications and mortality in thalassemia major patients.

Keywords Thalassemia major • Magnetic resonance imaging • Iron overload • Heart failure

Introduction

Thalassemia major (TM) represents one of the most serious and common genetic conditions, with 23 000 babies born every year.[1] TM is endemic in the Mediterranean basin, Sub-Saharan Africa, Middle East, Indian subcontinent, and Southeast Asia, but the consistent migrations of the last decades have considerably changed its epidemiology and nowadays the management of thalassemia patients is a global health issue. TM patients are subjected to continuous blood transfusions to improve chronic anemia[2] and iron-induced heart failure (HF) remains the main cause of mortality.[3,4]

The introduction of the T2* magnetic resonance imaging (MRI) technique as a robust and non-invasive method for the quantification of tissue iron has revolutionized the management of TM patients.[5,6]

In fact, this technique has made siderosis visible to both clinicians and patients and allowed the comparative evaluation of the efficacy of different chelation treatments, aimed to prevent iron accumulation or to eliminate iron deposition.[7] Commercially available chelators and their associations have been shown to differ not only in their administration, pharmacokinetics, adverse-effect profiles, and costs, but also in organ-specific iron removal.[8–11] Thus, MRI T2* has become key for tailored chelation therapies customized for each patient and for the assessment of the response to the chosen iron chelation regimen.[6]

Unfortunately, this strategy aimed at improving prognosis of iron-loaded patients, in many cases has been limited by MRI availability. In fact, the full clinical exploitation of the T2* MRI technique requires an easy, timely, and repeated access for the patient. Moreover, since T2* values may depend on the specific sequence and scanner as well as on the image analysis protocol, a standardization of the procedure is critical.[12,13] In Italy, there are about 5000 TM patients, and in order to achieve the previously described goals, the Myocardial Iron Overload in Thalassemia (MIOT) network has been developed in 2006. MIOT was a collaborative network among thalassemia and MRI centres that have agreed to share all clinical and instrumental data from the birth to the last MRI scan via a web-based database. The participation of several centres, homogeneously distributed across different regions, allowed not only to expand the availability of high-quality monitoring of iron accumulation, but also to decrease the mean distance covered by the patients to undergo the exam, increasing their comfort and reducing the associated cost.[14] These two aspects are not negligible considering the need for serial MRI monitoring, performed per protocol in the setting of the MIOT project every 18 ± 3 months. Moreover, the MIOT network introduced a new paradigm in myocardial iron overload (MIO) assessment: a segmental and global approach for quantifying myocardial iron distribution, validated also against biopsies.[15,16] Moreover, within the MIOT network, the multiparametric nature of cardiovascular magnetic resonance (CMR) has been exploited for the first time in TM patients by assessing MIO, biventricular function, and macroscopic myocardial fibrosis in the same scan.[16]

The aim of this study was therefore to evaluate the impact of the MIOT network after 10 years of activity on cardiac iron, complications, and deaths in TM patients.

Methods

Study population

Overall, 1746 TM patients (911 females; mean age 31.17 ± 9.09 years) were consecutively enrolled in the MIOT network and prospectively followed by the 70 thalassemia centres and the 10 MRI centres participating in the MIOT network (*Figure 1*). The clinical, instrumental, and laboratory data of the patients were recorded in the MIOT web-based database from birth and were updated at every MRI scan, performed per protocol every 18 ± 3 months.

All TM patients had been regularly transfused since early childhood and started undergoing chelation therapy from the mid-to-late 1970s, while patients born after the 1970s received chelation therapy from early childhood. MRI scanning was performed in the week immediately prior to scheduled blood transfusion.

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

Magnetic resonance imaging

All patients underwent MRI using 1.5 T scanners of three main vendors (GE Healthcare, Milwaukee, WI; Philips, Best, Netherlands; Siemens, Erlangen, Germany) equipped with phased-array coils. Breath-holding at end-expiration and ECG gating were used.

For iron overload assessment, multiecho T2* gradient–echo sequences were acquired. Intra- and inter-operator reproducibility and transferability among the MIOT MRI sites had been assessed previously.[17] For the heart, a multislice approach was used.[18] A mid-hepatic slice was obtained.[19] T2* image analysis was performed by trained MRI operators using a custom-written, previously validated software (HIPPOMIOT®). The global heart T2* value was obtained by averaging all 16 segmental T2* values, according to the standard American Heart Association (AHA) model.[20] The value of 20 ms was used as 'conservative' normal value for segmental and global T2* values.[21] Four patterns of MIO were identified: (i) no MIO (all segments with T2* ≥20 ms), (ii) heterogeneous MIO (some segmental T2* ≥20 ms and other segmental T2* <20 ms) and global heart T2* ≥20 ms, (iii) heterogeneous MIO and global heart T2* <20 ms, and (iv) homogeneous MIO (all T2* <20 ms).[18] Hepatic T2* values were calculated in a region of interest fixed in a homogeneous area of parenchyma without blood vessels.[19] Hepatic T2* values were converted into liver iron concentration (LIC).[22] An LIC of <3 mg/g/dw indicated no significant iron overload.[23]

Steady-state free precession cine images were acquired in sequential 8-mm short-axis slices from the atrio-ventricular ring to the apex to assess biventricular function parameters quantitatively in a standard way.[24] The inter-centre variability for the quantification of cardiac function had been previously reported.[25] Left ventricular dysfunction was diagnosed when left ventricular ejection fraction (LVEF) was below the previously defined cut-offs, specific for TM patients and normalized to sex and age.[24]

Late gadolinium enhancement (LGE) short- and long-axis views were acquired 8–18 min after gadobutrol (Gadovist®; Bayer; Berlin, Germany) intravenous administration at the standard dose of 0.2 mmol/kg using a fast gradient-echo inversion recovery sequence. Late gadolinium enhancement was considered present when visualized in two different views.[26] Late gadolinium enhancement images were not acquired in patients with a glomerular filtration rate <30 mL/min/1.73 m^2 and in patients who refused contrast-medium administration.

Follow-up for cardiovascular complications and deaths

For cardiac complications that occurred during the project, that is after baseline MRI was performed, the follow-up date coincided with the date of the last available MRI. For patients who did not perform a follow-up MRI, a case report form detailing patient outcomes between baseline MRI and September 2018 was completed by the caring haematologist.

The following events were considered: HF, arrhythmias, pulmonary hypertension (PH), myo/pericarditis, and vascular diseases. Heart failure was diagnosed by clinicians based on symptoms, signs, and instrumental findings according to the American College of Cardiology (ACC)/AHA guidelines.[27] Arrhythmias were diagnosed if documented by ECG or 24-h Holter ECG and if requiring specific medications. Arrhythmias were classified according to the ACC/AHA guidelines.[28] Pulmonary hypertension was diagnosed if tricuspid regurgitation velocity was >3.2 m/s on echocardiography.[29] In presence of clinical manifestations, the diagnosis of myo/pericarditis required confirmation by cardiac biomarkers (troponin), non-

Figure 1 MRI (light blue hearts) and thalassemia (purple circles) centres participating in the Myocardial Iron Overload in Thalassemia network.

invasive imaging modalities, and biopsy if indicated.[30] Vascular diseases included ischaemic stroke, non-fatal myocardial infarction defined as typical chest pain with elevated cardiac enzyme levels and with or without ST-segment elevation,[31] and peripheral vascular disease confirmed by diagnostic testing.[32]

Following the enrolment in the MIOT network, all deaths were retrieved by the section on serious adverse events in the database, where date and cause of death are specified.

Statistical analysis

All data were analysed using SPSS version 27.0 statistical package.

Continuous variables were described as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The normality of distribution of the parameters was assessed using the Kolmogorov–Smirnov test.

For continuous variables, the difference between baseline and last available values was analysed by Student's *t*-test for paired data or the Wilcoxon signed-rank test. For categorical variables, the paired comparison pre-MIOT vs. during-MIOT was performed using the McNemar's test.

Risk classes were defined based on the patterns of MIO from worst to normal: homogeneous MIO→heterogeneous MIO with global T2* <20 ms→heterogeneous MIO with global T2* ≥20 ms→no MIO.[16,18] For patients with baseline MIO (at least one segment with T2* <20 ms), improvement was defined as a transition to a lower risk class, stabilization was defined as no change in the risk class, and worsening was defined as a transition to a higher risk class. For patients with no MIO, worsening indicated the transition to a higher risk class.

Comparisons between groups were made by independent-samples *t*-test (continuous values with normal distribution) or Wilcoxon's signed rank test (continuous values with non-normal distribution).

The Cox proportional-hazard model was used to test the association between the considered covariates and cardiac mortality. The results were presented as hazard ratio (HR) with 95% confidence intervals (CI).

The Kaplan–Meier method was used to estimate and visualize the cumulative survival.

A two-tailed *P*-value of < 0.05 was considered statistically significant.

Results

Longitudinal changes in iron levels

A total of 355 (20.3%) patients performed only one MRI scan because their first MRI was arranged within the last 18 months of follow-up for this study, or they died or performed a follow-up MRI out of the MIOT network or refused a follow-up MRI scan. The 1392 TM patients who performed an end-of-study MRI were considered (726 females; mean age 31.13 ± 8.85 years). The mean interval between the first and last MRI was 4.35 ± 1.55 years (median 4.66 years).

At the last MRI, significantly higher cardiac T2* values (*Table 1*) and a significantly lower number of patients with global heart T2* <20 ms (11.9% vs. 26.4%, *P* < 0.0001) were detected (*Figure 2A*).

Figure 2B shows the frequency of the four MIO patterns at both scans. At the last CMR, a significantly higher frequency of patients with no MIO and a significantly lower frequency for the other three patterns indicating MIO were detected.

In the 767 patients who showed baseline MIO (400 heterogeneous MIO and global T2* ≥20 ms, 171 heterogeneous MIO and global T2*<20 ms, and 196 homogeneous MIO), the following changes were detected at follow-up: improvement in 524 (68.3%), stabilization in 219 (28.6%), and worsening in 24 (3.1%). Among the patients who worsened, 21.7% had an insufficient compliance.

Among the 625 patients with no baseline MIO, 119 (19.0%) showed at least one pathologic segment at follow-up, although 89.1% of them maintained a normal global heart T2* value.

MRI LIC values significantly decreased from baseline to follow-up MRI (*Table 1*).

The decrease in both cardiac and hepatic iron levels was significant also within each single group identified based on the time interval between the first and the last available MRI, and a higher improvement in heart iron was associated with longer follow-up.

The changes in global heart T2* showed a weak correlation with changes in MRI LIC (*R* = –0.196, *P* < 0.0001) and no correlation with baseline MRI LIC values (*R* = 0.020, *P* = 0.990).

There was a significant decrease in serum ferritin levels from 1576.37 ± 1550.23 ng/mL to 1440.33 ± 1516.69 ng/mL (*P* = 0.001). Changes in serum ferritin levels were positively correlated with changes in MRI LIC (*R* = 0.564, *P* < 0.0001) and negatively associated with changes in global heart T2* values (*R* = –0.248, *P* < 0.0001).

Longitudinal changes in biventricular function

Biventricular end-diastolic volume indexes were significantly lower at follow-up MRI while left ventricular LV mass index remained stable (*Table 1*). Left ventricular ejection fraction increased significantly at follow-up MRI in the whole study population and in the patient subgroups with a time interval between the two MRIs of 18 and 36 months.

In patients with baseline global heart T2* <20 ms, a significant increase in LVEF (difference: 3.15 ± 8.43%, *P* < 0.0001) as well as in right ventricular ejection fraction (RVEF, difference: 1.24 ± 8.98%, *P* = 0.002) was detected (*Figure 3*).

New occurrences of macroscopic myocardial fibrosis

A total of 611 patients received the contrast medium at both basal and last MRI scans. Among these, 121 patients (19.8%) had macroscopic myocardial fibrosis (two with ischaemic pattern) at baseline and myocardial fibrosis was detected in all of them also at follow-up. Patients without and with myocardial fibrosis at baseline MRI had comparable global heart T2* values (28.39 ± 11.99 ms vs. 27.40 ± 13.01 ms, *P* = 0.540).

At the last MRI, 113 (23.1%) new occurrences of myocardial fibrosis were detected, making the frequency of patients with myocardial fibrosis significantly higher than at basal MRI (38.3% vs. 19.8%, *P* < 0.0001). Patients who developed myocardial fibrosis during follow-up showed significantly lower baseline global heart T2* values than patients who remained always LGE-negative (24.76 ± 12.76 ms vs. 29.48 ± 11.56 ms, *P* = 0.001).

Chelation therapy

During the MIOT project, 47.3% of patients changed at least once the chelation regimen, that is switched to a different type of chelator or underwent dose/frequency modification.

The percentage of patients with good/optimal compliance was significantly higher at the last MRI than at baseline MRI (94.8% vs. 92.2%, *P* < 0.0001).

Patients who changed the chelation regimen were more likely to have a baseline global heart T2* <20 ms (34.1% vs. 20.8%, *P* < 0.0001) and to have a baseline LIC ≥3 mg/g/dw (68.2% vs. 58.3%, *P* < 0.0001).

Frequency of cardiac complications

The complete history of cardiac complications was retrieved for 1062 patients. Sixty-one patients were excluded because a pre-MIOT (before enrolment in the project) cardiac complication was still active at baseline MRI (28 arrhythmias, 20 HF, 9 PH, 3 myo/pericarditis, and 1 vascular disease).

Mean follow-up time for the considered 1001 patients with resolved cardiac complications or without cardiac complications before enrolment in the project was 56.24 ± 24.17 months (median 58.34 months). The frequency of patients with at least one cardiac complication significantly decreased after baseline MRI (*Table 2* and *Figure 4A*).

The frequency of HF significantly decreased after baseline MRI from 3.5 to 0.8% (*Figure 4B*). None of the eight patients who had an HF during the MIOT project had a previous history of HF. Mean time of onset from the time of the MRI scan to an HF episode was 30.05 ± 32.11 months and five episodes were recorded within 3 years. Compared with patients who remained HF-free, at baseline MRI, the patients who developed HF during the MIOT project had significantly different patterns of iron distribution (*P* = 0.039), with a significantly higher prevalence of patients with a homogeneous iron distribution (50.0% vs. 14.4%, *P* = 0.019) and significantly lower global heart T2* values (18.56 ± 13.47 ms vs. 29.01 ± 11.86 ms, *P* = 0.028). Moreover, they showed significantly lower LVEF (51.00 ± 13.24% vs. 61.73 ± 7.11%, *P* = 0.018) and RVEF (51.71 ± 13.59% vs.

Table 1 Changes between baseline and follow-up magnetic resonance imaging

Variable	Baseline	FU	Mean difference	*P*-Value
MRI LIC (mg/g/dw)				
All (*n* = 1392)	8.49 ± 10.01	6.89 ± 9.15	−1.61 ± 9.60	<0.0001
Last FU at 18 months (*n* = 179)	8.49 ± 10.04	6.89 ± 9.06	−1.59 ± 752	<0.0001
Last FU at 36 months (*n* = 296)	8.49 ± 10.39	7.26 ± 9.36	−1.23 ± 7.96	0.001
Last FU at 54 months (*n* = 471)	7.88 ± 8.66	6.85 ± 10.13	−1.04 ± 10.24	<0.0001
Last FU at 72 months (*n* = 446)	9.17 ± 11.01	6.68 ± 7.88	−2.48 ± 10.56	<0.0001
Global heart T2* (ms)				
All (*n* = 1392)	29.16 ± 12.02	35.44 ± 10.69	6.28 ± 10.37	<0.0001
Last FU at 18 months (*n* = 179)	30.60 ± 11.67	33.85 ± 10.92	3.25 ± 7.27	<0.0001
Last FU at 36 months (*n* = 296)	29.31 ± 11.88	34.53 ± 11.14	5.22 ± 9.14	<0.0001
Last FU at 54 months (*n* = 471)	30.27 ± 11.69	36.22 ± 10.37	5.95 ± 10.47	<0.0001
Last FU at 72 months (*n* = 446)	27.31 ± 12.39	35.85 ± 10.58	8.54 ± 11.59	<0.0001
No. segments with T2* <20 ms				
All (*n* = 1392)	4.59 ± 6.17	2.32 ± 4.74	−2.27 ± 5.26	<0.0001
Last FU at 18 months (*n* = 179)	3.89 ± 5.79	2.70 ± 4.97	−1.18 ± 3.72	<0.0001
Last FU at 36 months (*n* = 296)	4.44 ± 6.07	2.74 ± 5.08	−1.69 ± 4.71	<0.0001
Last FU at 54 months (*n* = 471)	4.09 ± 5.92	2.02 ± 4.48	−2.08 ± 5.02	<0.0001
Last FU at 72 months (*n* = 446)	5.51 ± 6.55	2.21 ± 4.65	−3.30 ± 6.15	<0.0001
Mid-septum T2* (ms)				
All (*n* = 1392)	30.61 ± 14.03	35.36 ± 11.79	4.75 ± 12.27	<0.0001
Last FU at 18 months (*n* = 179)	32.40 ± 14.69	34.87 ± 12.18	2.47 ± 9.96	<0.0001
Last FU at 36 months (*n* = 296)	30.93 ± 13.61	34.80 ± 12.56	3.87 ± 10.78	<0.0001
Last FU at 54 months (*n* = 471)	31.61 ± 13.77	36.09 ± 11.45	4.48 ± 12.95	<0.0001
Last FU at 72 months (*n* = 446)	28.64 ± 14.13	35.17 ± 11.46	6.53 ± 13.08	<0.0001
LVEDVI (mL/m^2)				
All (*n* = 1392)	87.66 ± 19.33	84.87 ± 19.25	−2.79 ± 16.29	<0.0001
Last FU at 18 months (*n* = 179)	89.35 ± 18.98	86.70 ± 17.34	−2.65 ± 12.70	0.010
Last FU at 36 months (*n* = 296)	86.24 ± 17.96	84.24 ± 17.80	−2.00 ± 15.52	0.048
Last FU at 54 months (*n* = 471)	88.21 ± 18.63	85.52 ± 19.00	−2.69 ± 15.11	<0.0001
Last FU at 72 months (*n* = 446)	87.33 ± 20.91	83.91 ± 20.89	−3.42 ± 18.93	<0.0001
LV mass index (g/m^2)				
All (*n* = 1392)	58.57 ± 14.29	58.04 ± 15.15	−0.53 ± 14.31	0.246
Last FU at 18 months (*n* = 179)	60.39 ± 18.01	60.29 ± 14.66	−0.09 ± 15.78	0.608
Last FU at 36 months (*n* = 296)	60.42 ± 14.99	59.51 ± 16.27	−0.92 ± 14.45	0.236
Last FU at 54 months (*n* = 471)	58.63 ± 12.98	58.68 ± 13.88	0.05 ± 12.83	0.607
Last FU at 72 months (*n* = 446)	56.68 ± 13.32	55.63 ± 15.89	−1.05 ± 15.08	0.073
LVEF (%)				
All (*n* = 1392)	61.12 ± 6.22	61.86 ± 6.96	0.74 ± 7.66	0.002
Last FU at 18 months (*n* = 179)	60.73 ± 7.57	62.55 ± 7.32	1.82 ± 6.62	0.003
Last FU at 36 months (*n* = 296)	60.65 ± 7.77	61.81 ± 7.28	1.16 ± 8.39	0.039
Last FU at 54 months (*n* = 471)	61.99 ± 6.78	62.52 ± 6.82	0.53 ± 7.64	0.138
Last FU at 72 months (*n* = 446)	60.68 ± 6.77	60.95 ± 6.68	0.28 ± 7.55	0.651
RVEDVI (mL/m^2)				
All (*n* = 1392)	83.33 ± 20.52	81.78 ± 20.50	−1.55 ± 18.63	<0.0001
Last FU at 18 months (*n* = 179)	83.82 ± 19.44	82.79 ± 16.89	−1.03 ± 15.97	0.612
Last FU at 36 months (*n* = 296)	81.30 ± 25.21	81.96 ± 20.87	0.65 ± 24.74	0.258
Last FU at 54 months (*n* = 471)	83.80 ± 19.07	82.39 ± 20.25	−1.40 ± 16.01	0.013
Last FU at 72 months (*n* = 446)	83.91 ± 19.09	80.67 ± 21.76	−3.24 ± 17.57	<0.0001
RVEF (%)				
All (*n* = 1392)	61.12 ± 7.93	60.74 ± 8.24	−0.38 ± 9.03	0.605
Last FU at 18 months (*n* = 179)	61.02 ± 8.33	62.05 ± 8.19	1.03 ± 7.82	0.063
Last FU at 36 months (*n* = 296)	60.28 ± 8.82	60.09 ± 8.85	−0.18 ± 9.18	0.866

Continued

Table 1 *Continued*

Variable	Baseline	FU	Mean difference	*P*-Value
Last FU at 54 months ($n = 471$)	62.38 ± 7.34	61.63 ± 8.05	−0.75 ± 9.11	0.270
Last FU at 72 months ($n = 446$)	60.39 ± 7.63	59.74 ± 7.93	−0.66 ± 9.26	0.330

FU, follow-up; LIC, liver iron concentration; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction.

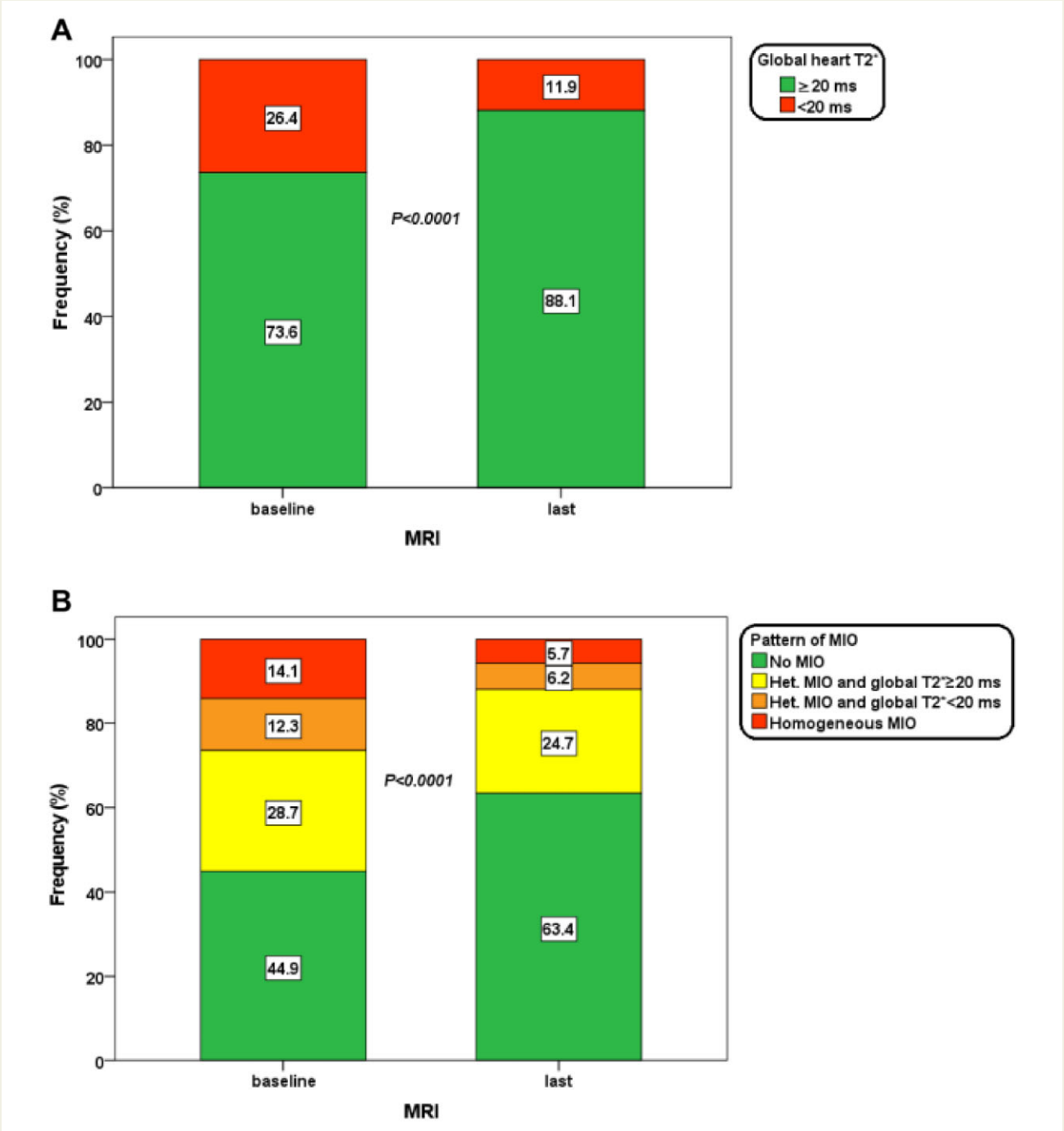


Figure 2 Changes in cardiac iron levels between baseline and last cardiovascular magnetic resonance scan based on global heart T2* values (*A*) and patterns of myocardial iron overload (*B*).

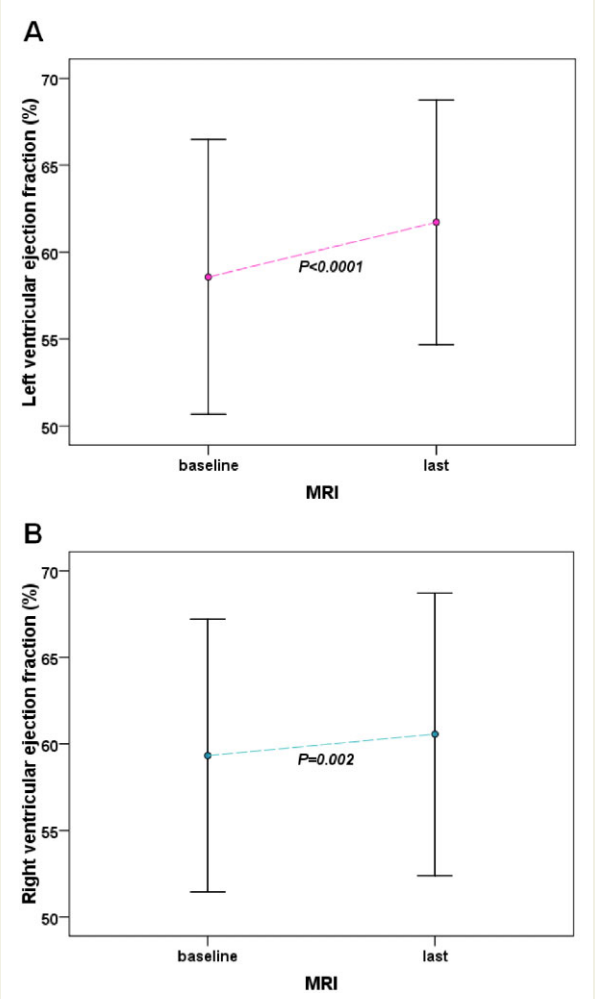


Figure 3 Changes in left ventricular (*A*) and right ventricular (*B*) ejection fraction in patients with baseline global heart T2* <20 ms.

61.59 ± 7.78%, $P = 0.023$), and a significantly higher frequency of myocardial fibrosis (50.0% vs. 15.7%, $P = 0.022$). To have a more comparable pre- and during MIOT timeframe, we considered only HF that occurred after the year 2000. The frequency of pre-MIOT HF became 2.9%, that remained significantly higher than the frequency of HF during the MIOT project ($P = 0.001$).

The frequency of arrhythmias, for the majority supraventricular, did not change after baseline MRI. Compared with patients free of arrhythmias, patients who developed arrhythmias during the project had comparable baseline global heart T2* values, biventricular volumes, and LVEF, but significantly lower RVEF (57.25 ± 9.68% vs. 61.65 ± 7.78%, $P = 0.0029$) and higher left and right atrial areas indexed to body surface area (15.79 ± 3.16 cm^2/m^2 vs. 12.78 ± 2.47 cm^2/m^2, $P < 0.0001$ and 13.29 ± 3.26 cm^2/m^2 vs. 11.94 ± 2.24 cm^2/m^2, $P = 0.047$, respectively).

Deaths

Information on death was available for 1688 (96.7%) patients. Forty-six died during the study (*Figure 5*). Overall, all-cause 1-, 5-, and 10-year survival rates after enrolment in the MIOT project were 99.1%, 97.5%, and 92.0%, respectively.

Table 2 Frequency of cardiac complications

Cardiac complications	Before enrolment in MIOT project	During MIOT project	*P*-Value
Cardiovascular complications	66 (6.6)	44 (4.4)	0.023
Heart failure	35 (3.5)	8 (0.8)	<0.0001
Arrhythmias	25 (2.5)	35 (3.1)	0.418
Pulmonary hypertension	2 (0.2)	1 (0.1)	1.000
Vascular diseases	6 (0.6)	2 (0.2)	0.289
Myo/pericarditis	4 (0.4)	3 (0.3)	1.000

Values are given as *n* (%).
MIOT, Myocardial Iron Overload in Thalassemia.

Heart failure was the leading cause of death, accounting for 34.8% of all causes. No patients died due to arrhythmias.

Patients who died from a cardiac cause had significantly lower baseline global heart T2* values (18.08 ± 14.03 ms vs. 27.78 ± 14.55 ms, $P = 0.030$) and baseline LVEF (51.56 ± 15.97% vs. 61.48 ± 10.02%, $P = 0.032$) and significantly higher baseline MRI LIC (23.96 ± 28.29 mg/g dw vs. 7.52 ± 8.94 mg/g dw, $P = 0.004$) than patients who died from another cause. The risk of cardiac death was more than four times greater in patients with a baseline global heart T2* <20 ms than in patients with a normal baseline global heart T2* value (HR: 4.24, 95% CI: 1.73–10.47; $P = 0.002$) (*Figure 6*) and more than three times greater in patients with baseline left ventricular dysfunction than in patients with a normal baseline LVEF (HR: 3.19, 95% CI: 1.29–7.87; $P = 0.011$).

Nine deaths were due to cancer (four hepatocellular carcinoma, one pancreatic adenocarcinoma, one metastatic cancer of unknown primary site, one renal cancer, one leukaemia, and one lymphoma), representing the second leading cause of death.

Discussion

Networking is recommended for improving research and consequently the clinical patients' management, particularly in rare diseases. The MIOT network was the first collaborative network involving clinical and MRI centres using homogeneous standard procedures for ensuring repeatable cardiac and liver iron quantifications close to home.[14] The creation of this validated network has led to a significant increase of the number of Italian patients undergoing T2* evaluation. According to the MIOT protocol, TM patients performed a MRI scan every 18 ± 3 months, balancing the monitoring recommendations according to the basal cardiac iron status[6] and the real availability for MRI scans in Italy.[14] Today, the MIOT network is recognized as the depository of one of the largest databases in thalassemia around the world.[33] The present study describes the impact of the 10-year activity of the MIOT network on cardiac outcomes of TM patients.

We prospectively demonstrated a significant reduction in cardiac iron burden, most likely resulting from the use of T2* MRI that

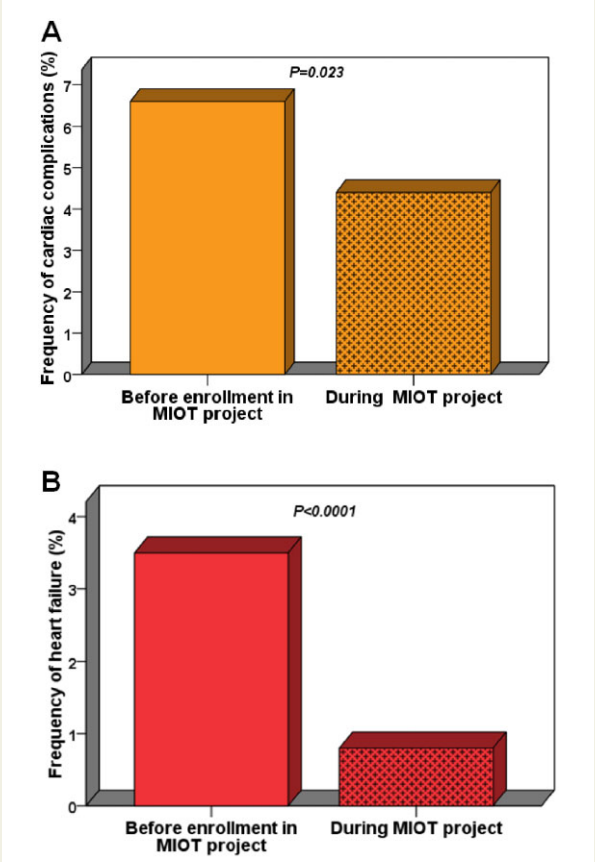


Figure 4 Frequency of overall cardiac complications (*A*) and of heart failure (*B*) before and after patient enrolment in the Myocardial Iron Overload in Thalassemia project.

allowed reliable identification of patients with myocardial siderosis, triggering an appropriate change or intensification of iron chelation treatment. Indeed, almost half of our patients changed the chelation regimen (drug or frequency/dosage) during the project based on T2* MRI reports, and these patients showed more frequently significant MIO at baseline, confirming how the use of a networked approach to care has facilitated this strategical goal (*Graphical Abstract*).

Improvements in myocardial iron were not related to baseline LIC and were only weakly correlated with improvements in LIC and serum ferritin levels. These findings further reinforce the need to quantify iron status in the different organs over time.

Improvements in myocardial iron were concordant with significant improvements in biventricular global systolic function, specifically in patients with significant heart iron at baseline.

Our longitudinal data showed that macroscopic myocardial fibrosis is not reversible in TM. In agreement with previous retrospective studies on adult TM patients, no cross-sectional association was detected between myocardial fibrosis and cardiac iron,[26,34] but the patients who developed fibrosis after baseline CMR had significantly lower baseline global heart T2* values. Of note, in paediatric TM patients, free of risk factors for myocardial fibrosis, such as diabetes mellitus and hepatitis C virus infection, a significant cross-sectional and prospective link between heart iron and replacement myocardial fibrosis has been detected.[35,36] All these findings suggest that cardiac iron overload is one of the main determinants of myocardial fibrosis in TM, but while iron could be removed by intensive chelation treatment, the induced heart damage in terms of fibrosis does not regress and it is associated with the development of HF based on our 10-year networking data. In the current era, in TM, myocardial fibrosis has been demonstrated to be a predictor of cardiac complications stronger than MIO,[16] probably reflecting the prompt MRI-tailored chelation therapy and the weak MRI-tailored cardio-active therapy. The high number of new occurrences during the follow-up showed by our data (nearly one-quarter of the assessed patients) strengthens the importance of repeating contrast CMR over time[37,38] and referring TM patients to cardiologists.

The improvements in cardiac iron and function resulted in a significant reduction in the frequency of HF. Indeed, MIO and its distribution, and left ventricular dysfunction were shown to be strong independent predictors of HF[16,39] and a small increase in LVEF was shown to be associated with a significantly reduced risk of HF development within 12 months.[40] We did not detect a decrease in the frequency of arrhythmias, for the majority supraventricular. This finding is concordant with the evidence that MIO contributes less to the development of supraventricular arrhythmias than to cardiac failure, as previously reported.[16,25,39] Accordingly, the patients who developed arrhythmias during the project and the patients who remained arrhythmia-free had comparable baseline global heart T2* values.

Our study showed that HF continues to be the leading cause of death (35% of all causes) also in well treated TM patients. Importantly, we detected a significant decline in HF-related mortality, which was 60.2% in an Italian study dated 2004 and conducted before the homogeneous introduction of the T2* MR by the MIOT network.[3] As suggested from the UK experience,[4] after the introduction of oral iron chelators, and especially of the cardioprotective deferiprone,[41,42] MRI can be considered the main driver for the improvement in cardiac mortality. Conversely, in comparison with the above-mentioned Italian study,[3] we detected a consistent increase in the frequency of deaths due to malignancies (from 3.6 to 19.6%), indirectly reflecting the reduction in deaths due to MIO and the increased life expectancy.

In recent years, the native T1 mapping technique has been proposed as a complementary tool to the T2* technique, thanks to its improved sensitivity in detecting changes associated with mild or early MIO.[43,44] The MIOT network is well-suited to test in the next years the transferability of T1 mapping among different centres and to assess its predictive value for cardiac outcomes in TM.

Conclusion

Over 10 years, within the MIOT network, the continuous and standardized monitoring of cardiac iron levels and a tailored chelation therapy resulted in a reduction of MIO in almost 70% of patients, with improvement of cardiac function and reduction of cardiac complications and mortality from MIO-related HF. A national clinical and imaging networking in rare diseases was therefore effective in improving the care and reducing the cardiac burden in TM patients. Further spreading of the MIOT network and addressing iron burden

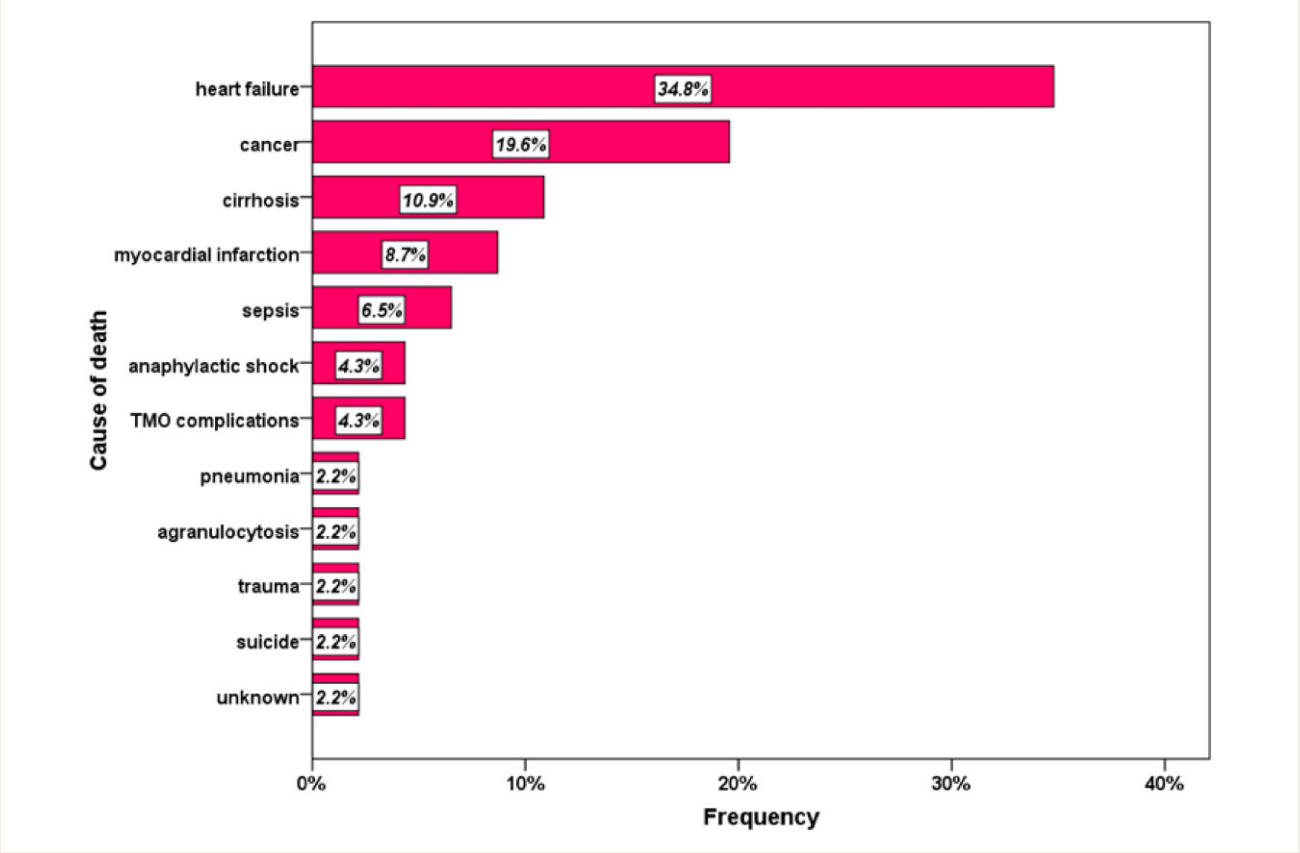


Figure 5 Causes of death in patients enrolled in the Myocardial Iron Overload in Thalassemia project.

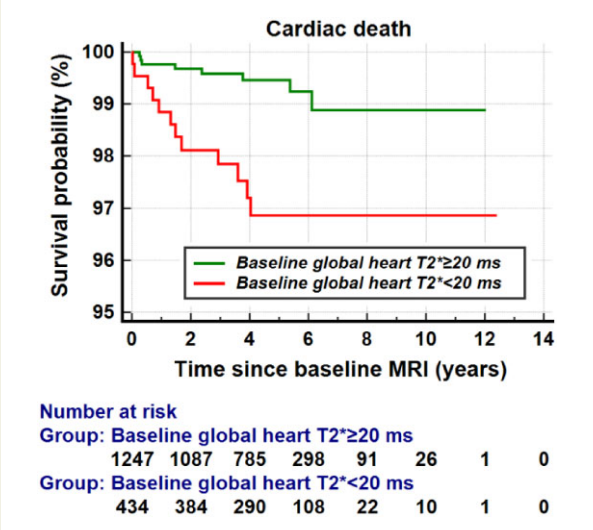


Figure 6 Kaplan–Meier survival curve for cardiac mortality in patients with normal and pathological global heart T2* values at baseline magnetic resonance imaging.

in other critical organs, such as the pancreas,[45] are recommended to improve the prognosis and quality of life in thalassemia.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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