



RESEARCH ARTICLE

**REVISED** The relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions, hepatic and cardiac iron siderosis among Egyptian children and young adults with  $\beta$ -thalassaemia major and sickle cell disease: a cross-sectional study [version 2; peer review: 2 approved]

Previously titled: "Iron overload parameters and early detection of cardiac disease among Egyptian children and young adults with  $\beta$ -thalassaemia major and sickle cell disease: a cross-sectional study"

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**v2** First published: 09 Sep 2020, 9:1108  
<https://doi.org/10.12688/f1000research.25943.1>  
 Latest published: 07 Jun 2021, 9:1108  
<https://doi.org/10.12688/f1000research.25943.2>

**Abstract**

**Background:** Cardiac, hepatic and pancreatic T2\* measured by magnetic resonance imaging (MRI) has been proven to be an accurate and non-invasive method for measuring iron overload in iron overload conditions. There is accumulating evidence that pancreatic iron can predict cardiac iron in young children because the pancreas loads earlier than the heart. The aim of our study was to assess the relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions and liver and cardiac iron among patients with  $\beta$ -thalassaemia major ( $\beta$ TM) and sickle cell disease (SCD).  
**Methods:** 40  $\beta$ TM and 20 transfusion-dependant SCD patients were included along with 60 healthy age and sex-matched controls. Echocardiography and Tissue Doppler Imaging were performed for all subjects as well as the control group. Hepatic, cardiac and pancreatic iron overload in cases were assessed by MRI T2\*.  
**Results:** The mean age of our patients was 13.7 years with mean frequency of transfusion/year 12. Mean cardiac T2\* was 32.9 ms and

**Open Peer Review**

**Reviewer Status**

	Invited Reviewers	
	1	2
<b>version 2</b> (revision) 07 Jun 2021		 report
<b>version 1</b> 09 Sep 2020	 report	  report

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mean myocardial iron concentration was 0.7 mg/g; One patient had cardiac iron overload of moderate severity. Mean pancreatic T2\* was 22.3 ms with 20 patients having mild pancreatic iron overload. Pancreatic T2\* correlated positively peak late diastolic velocity at septal mitral annulus ( $r=0.269$ ,  $p=0.038$ ), peak early diastolic velocity at tricuspid annulus ( $r=0.430$ ,  $p=0.001$ ) and mitral annular plane systolic excursion ( $r=0.326$ ,  $p=0.01$ ); and negatively with end systolic pulmonary artery pressure ( $r=-0.343$ ,  $p=0.007$ ) and main pulmonary artery diameter (MPA) ( $r=-0.259$ ,  $p=0.046$ ). We couldn't test the predictability of pancreatic T2\* in relation to cardiac T2\* as only one patient had cardiac T2\* $<20$  ms.

**Conclusion:** There was a relationship between pancreatic iron siderosis with cardiac dysfunction in multi-transfused patients with  $\beta$  TM and SCD. No direct relation between pancreatic iron and cardiac siderosis was detected.

### Keywords

Iron overload, pancreatic iron, Thalassemia major, Sickle cell disease, Tissue Doppler Imaging

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Any reports and responses or comments on the article can be found at the end of the article.

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**Author roles:** Salama K: Supervision; Abdelsalam A: Supervision; Eldin HS: Supervision; Youness E: Methodology; Selim Y: Investigation; Salama C: Writing – Review & Editing; Hassanein G: Writing – Original Draft Preparation; Samir M: Writing – Review & Editing; Zekri H: Validation

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

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**How to cite this article:** Salama K, Abdelsalam A, Eldin HS *et al.* **The relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions, hepatic and cardiac iron siderosis among Egyptian children and young adults with  $\beta$ -thalassaemia major and sickle cell disease: a cross-sectional study [version 2; peer review: 2 approved]** F1000Research 2021, 9:1108 <https://doi.org/10.12688/f1000research.25943.2>

**First published:** 09 Sep 2020, 9:1108 <https://doi.org/10.12688/f1000research.25943.1>

**REVISED Amendments from Version 1**

1. The title has been modified
2. Some text modifications have been made to the abstract and r-values have been added to the results section of the abstract
3. Some text modifications have been made to the introduction
4. Classification of patients according to LIC has been added to patients and methods section
5. The title of Table 3 has been modified
6. The first 3 sentences of the discussion including aim of the study have been removed

**Any further responses from the reviewers can be found at the end of the article**

## Introduction

The hallmark of chronic hemolytic anemias (CHAs) is premature destruction of erythrocytes<sup>1</sup>. In Egypt, the common forms of inherited CHAs include  $\beta$ -thalassemia major ( $\beta$ TM) and sickle cell disease (SCD)<sup>2</sup>. The main lines of therapy is blood transfusion and iron chelation. Quality of life and life expectancy have markedly improved since the introduction of oral iron chelators. However, death from cardiomyopathy and heart failure in these patients remains high, possibly because of the heavy transfusion burden<sup>3</sup> or the generation of reactive oxygen species induced by excess iron<sup>4</sup>.

Consequently, it is important to detect silent cardiac dysfunction early before the development of symptomatic heart disease<sup>5</sup>. Currently, several methods have been used in clinical studies for the determination of cardiac affection in iron overload conditions. Meanwhile, their uses are limited in  $\beta$ TM and SCD patients due to controversy on their reliability as well as their high cost. The aim of this study was to assess the relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions and liver and cardiac iron in multi-transfused Egyptian patients with  $\beta$ TM and SCD.

## Methods

### Patients

40  $\beta$ TM and 20 SCD patients aged  $\geq 7$  years with the onset of regular transfusions before the age of 2 years and receiving regular transfusions ( $\geq 3$  transfusions per year with total volume ranging from 100 to 150 cc/kg/year according to Gale *et al.*, 2011)<sup>6</sup> following up at the hematology outpatient clinic, Cairo University Children's Hospital, Cairo, Egypt during the study period (from June, 2017 to June, 2018) were enrolled in the study.

Patients with congenital or acquired heart diseases, hypertension, heart failure, cardiac drug usage, known risk factors for secondary pulmonary hypertension, acute febrile illness at enrollment or those with contraindications or inability to undergo magnetic resonance imaging (MRI) without sedation were excluded.

In addition, 60 healthy subjects with the same age and gender referred to our hospital for routine checkup were selected as the control group.

Demographics, transfusion history, and information concerning iron chelation and therapy were obtained by through patient interview during routine check-ups and chart review. Labs, including complete blood picture with blood indices, reticulocytic count and serum ferritin, were performed as routine labs done during check-ups.

The study was approved by the ethics and scientific research committee of Cairo University, Faculty of Medicine (ethical clearance number, I-060317) and the study was conducted in accordance with Cairo University's laws for human research. Written informed consent was obtained from participants and parent/guardians in the case of children <18 years. Assent was obtained in addition from children <18 years.

### Cardiac T2\*

All patients were scheduled for cardiac, hepatic and pancreatic MRI T2\* at the Radiology Department, using a Philips Achiva, Netherland (1.5 Tesla) superconducting magnet with a Torso XL coil.

Scans were synchronized to the cardiac cycle using standard electrocardiogram gating. We then took a single 10 mm-thick short axis, mid ventricular slice positioned half way between the base and the apex of the left ventricle with repetition time (TR) 20 ms and multiple echo times (TEs) (2.4, 4.6, 6.8, 9.1 and 11.3ms). Flip angle 30 and field of view (FOV) 320 mm. A fitting curve algorithm using a monoexponential decay with a constant offset ( $S=S_0e^{-TE/R_2^*+C}$ ; S is the signal intensity, S<sub>0</sub> is the signal intensity at TE=0 ms, and C is a constant) was applied to determine the T2\* value. Results of cardiac T2\* and myocardial iron concentration (MIC) measurements were considered as discontinuous variables and were classified as follows: normal iron concentration (T2\* >20, MIC < 1.16 mg/g), light (T2\* 15–20, MIC 1.16– 1.65 mg/g), moderate (T2\* 10–15, MIC 1.65– 2.71 mg/g) and severe (T2\* <10, MIC > 2.71 mg/g)<sup>7</sup>.

### Liver and pancreas T2\*

The liver T2\* was measured by imaging a single trans-axial slice (10 mm) through the center of the liver. The pancreas T2\* was measured by imaging a single trans-axial slice (10 mm) through the head of the pancreas with TR 20 ms and multiple TEs (2.4, 4.6, 6.8, 9.1 and 11.3ms) as well as through the body and mean region of interest was taken. Results of hepatic and pancreatic T2\* measurements were considered as discontinuous variables and were classified as follows: normal iron concentration (T2\* >11.4, liver iron concentration (LIC) < 2 mg/g), light (T2\* 3.8–11.4, LIC 2.0– 7.0 mg/g), moderate (T2\* 1.8–3.8, LIC 7.0–15.0 mg/g) and severe (T2\* <1.8, LIC > 15 mg/g)<sup>8</sup>.

We divided our patients into two groups according to LIC, normal <7 mg/g or overload >7 mg/g.

### Echocardiography examination

Trans-thoracic two dimensional (2D) guided (M mode) and doppler echocardiogram were performed with a Hewlett-Packard 5500 SONOS ultrasonic machine phased array sector scanner with the 4 and 8 MHZ probes according to age. M-mode, 2D and doppler echocardiographic parameters were averaged over three cardiac cycles and all echocardiographic measurements were performed according to the guidelines for performance of echocardiogram by American Society of Echocardiography<sup>9</sup>. Tissue Doppler Imaging was performed for all patients and 60 – age and sex-matched – healthy subjects as a control group. Systolic function was assessed through measuring peak systolic (S') myocardial velocities at both the septal and lateral mitral and free-wall tricuspid annulus. Diastolic function was assessed through measuring peak early diastolic (E') and peak late diastolic (A') myocardial velocities at both the septal and lateral mitral and free-wall tricuspid annulus. The ratio of E to E' velocity (E/E') was computed as a surrogate of LV filling pressure<sup>10</sup>.

### Statistical analysis

The statistical package SPSS version 25 was used for data analysis. Mean, SD, and range were used for describing quantitative variables. The  $\chi^2$  test was used to compare qualitative variables between groups. The t-test was used to compare quantitative variables in parametric data. The Mann-Whitney test was used instead of the t-test for nonparametric data. Univariate correlations among the biological markers of iron metabolism and MRI LIC will be studied with Spearman's rank-order correlation coefficient. Receiver-operator characteristic (ROC) curves will be used to analyze the capacity of serum ferritin to predict MRI-based hepatic iron overload, and to identify optimal test and threshold values. P-values <0.05 was considered significant and P values <0.01 were considered highly significant.

### Results

In total, 40  $\beta$ TM, 20 SCD and 60-age and sex matched subjects were included in the study. The study group consisted of 33 (55%) men and 27 (45%) women. Their mean age was

13.7 ( $\pm$ 4.4) years and mean age at diagnosis was 12.4 ( $\pm$ 8.6) months. A total of 40 (66.7%) patients were splenectomised (33 with  $\beta$ TM and 7 with SCD), and 58 patients (96.7%) were receiving a chelator (39  $\beta$ TM; 19 SCD; p=0.6) for a duration ranging from 6 to 120 month (median 48 months). Assessment of the iron overload status of the studied patients revealed that 34 (56.7%) patients had average serum ferritin exceeding 2500 ng/ml, 10 (16.7%) had LIC  $\geq$ 7 mg Fe/g dry liver weight (dw), 20 patients (33.3%) showed mild pancreatic iron overload and only one patient had evidence of cardiac iron overload of moderate severity (Figure 1). Other demographic and laboratory data are illustrated in Table 1.

Investigating the relation between different iron overload parameters revealed that serum ferritin correlated negatively with pancreatic T2\* and positively with LIC. We divided our patients into two groups according to LIC, normal <7 or overload >7 (LIC is our gold standard), and this was plotted against pancreatic T2\* using ROC curve. We found that area under the curve of pancreatic T2\* was 0.851 (95% CI: 0.757–0.945). The sensitivity of pancreatic T2\* in predicting LIC was 82% and specificity was 80% at a cutoff value  $\geq$ 10.1 (Figure 2). We failed to test the predictability pancreatic T2\* in relation to cardiac T2\* as nearly all patients have cardiac T2 > 20 and only. One patient has cardiac T2 < 20. ROC curve analysis couldn't be done.

Echocardiographic assessments of the studied  $\beta$ TM and SCD patients were compared to the control group and the results are illustrated in Table 2. Mitral E/A ratio >2 was found in 18 (30%) patients indicating diastolic dysfunction of restrictive pattern. None of our patients had a mitral E/A ratio <1 denoting that none of them had diastolic dysfunction of impaired relaxation pattern. Statistically significant differences between patients and controls were detected in late diastolic myocardial velocities (A) and systolic myocardial velocities (S) at the basal mitral annulus of the lateral and septal walls being higher in patients than controls. Also peak systolic velocity at the tricuspid annulus of patients was significantly higher than controls (Table 2).

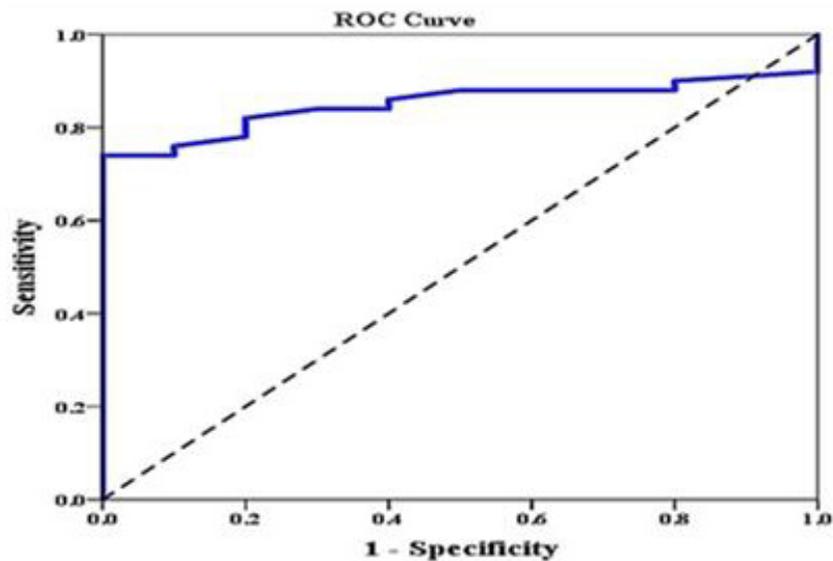


**Figure 1. Magnetic resonance imaging of a patient with moderate cardiac iron overload, normal hepatic and pancreatic iron concentration. a)** Calculated myocardial T2\* equals 13.3 ms and myocardial iron concentration equals 1.91 mg/g (moderate cardiac iron overload). **b)** Calculated hepatic T2\* equals 26.5 ms and liver iron concentration equals 0.60 mg /g (no hepatic iron overload). **c)** Calculated pancreatic T2\* equals 40 ms (no pancreatic iron overload). *Conclusion:* The patient has moderate cardiac iron overload, normal hepatic and pancreatic iron concentration.

**Table 1. Clinical, laboratory and iron profile data of the studied patients.** Data are expressed as mean±SD (range).

Parameters	Study group (n=60)	β-thalassaemia major (n=40)	Sickle cell disease (n=20)	P-VALUE
Age (years)	13.7 ± 4.4 (7 - 24)	14.3 ± 4.5 (7 - 20)	12.6 ± 4.2 (7 - 24)	0.083
Male/Female	33/27	20/20	13/7	0.279
Weight (kg)	-1.1 ± 0.8 (-3 to 1)	-1.2 ± 0.8 (-3 - 0.7)	-1 ± 0.9 (-2.7 - 1)	0.409
Height (m)	-1.5 ± 1.5 (-6.3 - 5)	-1.5 ± 1.7 (-6.3 - 5)	-1.3 ± 1 (-3 - 0.8)	0.869
Hemoglobin (g/dl)	7.1 ± 1.4 (4.5 - 13.2)	6.9 ± 1.1 (4.5 - 9.3)	7.6 ± 1.8 (5.4 - 13.2)	0.246
Platelets (/mm <sup>3</sup> )	568.8 ± 290.3 (143 - 1324)	650.3 ± 282.1 (203 - 1324)	405.8 ± 237.5 (143 - 978)	0.001*
Serum ferritin (ng/ml)	3248.9 ± 2546.2 (200.9 - 13800)	3737.2 ± 2845.5 (719.2 - 13800)	2272.2 ± 1416.5 (200.9 - 6036)	0.050*
Liver iron concentration (mg/g)	4.7 ± 2.6 (0.6 - 11.7)	4.8 ± 2.7 (0.6 - 11.7)	4.4 ± 2.4 (0.6 - 8.5)	0.906
Hepatic T2*(ms)	8 ± 6.2 (2.3 - 26.5)	7.4 ± 5.1 (2.3 - 25)	9.2 ± 8 (3.1 - 26.5)	1.000
Cardiac T2*(ms)	32.9 ± 12.4 (13.3 - 102.1)	32 ± 9.1 (20.3 - 60.6)	34.7 ± 17.5 (13.3 - 102.1)	0.605
Myocardial iron concentration (mg/g)	0.7 ± 0.3 (0.1 - 1.9)	0.7 ± 0.2 (0.1 - 1.2)	0.7 ± 0.3 (0.2 - 1.9)	0.500
Pancreatic T2* (ms)	22.3 ± 17.5 (4.5 - 116)	17.1 ± 11.7 (4.5 - 50.7)	32.6 ± 22.5 (5.7 - 116)	<0.0001*

\*Statistically significant, ms=millisecond, SD=Standard deviation.



**Figure 2.** ROC curve analysis to explore the discriminant ability of pancreatic T2 in differentiating those with high liver iron concentration (LIC) (>7) from those with low LIC (<7).

**Table 2. Echocardiographic and Tissue Doppler Imaging data of the studied patients and controls.** Data are expressed as mean±SD (range).

Parameter	βTM (n=40)	SCD (n=20)	Control (n=60)	P-VALUE
FS	41.2 ± 5.8 (30 - 55)	40.1 ± 8.3 (30 - 55)	40.7 ± 3.4 (34 - 45)	0.779
EF	71.6 ± 6.5 (58 - 83)	69.7 ± 8.9 (58 - 83)	70.8 ± 5.8 (58 - 79)	0.792
TAPSE (mm)	28.6 ± 6.1 (9 - 37)	30.8 ± 3.8 (25 - 37)	22.1 ± 2.8 (14 - 27)	<0.0001*
MAPSE (mm)	18.1 ± 2.7 (15 - 25)	16.7 ± 2.7 (15 - 25)	16.2 ± 1.9 (12 - 20)	0.019*
ESPAP (mmHg)	32.1 ± 7.7 (20 - 44)	28.4 ± 9 (18 - 44)	21.3 ± 3.9 (17 - 32)	<0.0001*
Mitral E/E'	6.9 ± 1.93 (3.5 - 10.8)	5.97 ± 2.49 (3.5 - 11)	6.83 ± 1.47 (4 - 11)	0.060
Mitral E/A	1.9 ± 0.6 (1.1 - 2.9)	1.7 ± 0.5 (1.1 - 2.8)	1.3 ± 0.3 (0.8 - 2)	<0.0001*
Mitral annular velocity (septal annulus)				
E'(m/sec)	0.15 ± 0.03 (0.08 - 0.19)	0.15 ± 0.01 (0.11 - 0.17)	0.15 ± 0.03 (0.11 - 0.19)	0.457
A'(m/sec)	0.08 ± 0.04 (0.03 - 0.18)	0.1 ± 0.04 (0.06 - 0.18)	0.07 ± 0.01 (0.05 - 0.08)	0.031*
S'(m/sec)	0.08 ± 0.02 (0.04-0.13)	0.09 ± 0.02 (0.06 - 0.13)	0.07 ± 0.01 (0.06 - 0.09)	0.004*
Mitral annular velocity (lateral annulus)				
E'(m/sec)	0.17 ± 0.04 (0.11 - 0.28)	0.19 ± 0.04 (0.15 - 0.28)	0.16 ± 0.01 (0.13 - 0.18)	0.068
A'(m/sec)	0.1 ± 0.06 (0.04 - 0.22)	0.11 ± 0.05 (0.06 - 0.22)	0.06 ± 0.01 (0.05 - 0.1)	<0.0001*
S'(m/sec)	0.09 ± 0.02 (0.05 - 0.14)	0.1 ± 0.02 (0.06 - 0.13)	0.08 ± 0.01 (0.07 - 0.09)	0.005*
Tricuspid annular velocity				
E'(m/sec)	0.16 ± 0.06 (0.06 - 0.28)	0.18 ± 0.05 (0.12 - 0.28)	0.18 ± 0.02 (0.15 - 0.2)	0.183
A'(m/sec)	0.12 ± 0.05 (0.03 - 0.19)	0.12 ± 0.05 (0.06 - 0.19)	0.12 ± 0.01 (0.1 - 0.14)	0.986
S'(m/sec)	0.13 ± 0.04 (0.04 - 0.21)	0.14 ± 0.04 (0.08 - 0.21)	0.12 ± 0.01 (0.1 - 0.16)	0.006*

\*Statistically significant, **ms**=millisecond, **βTM**=Beta thalassemia major, **SCD**=Sickle cell disease, **LIC**=Liver iron concentration, **MIC**=Myocardial iron concentration, SD=Standard deviation. **FS**=Fractional shortening, **EF**=Ejection fraction, **Mitral E/A**=Ratio of the peak velocity of early diastolic transmitral flow to the peak velocity of the late diastolic transmitral flow, **TAPSE**=Tricuspid annular plain systolic excursion, **MAPSE**=Mitral annular plane systolic excursion, **ESPAP**=End systolic pulmonary artery pressure, **Mitral E/ E'**= Ratio of the peak velocity of early diastolic transmitral flow to early diastolic mitral annular velocity, **Mitral E/A**=Ratio of the peak velocity of early diastolic transmitral flow to the peak velocity of the late diastolic transmitral flow **S'**=Peak systolic velocity, **E'**=Peak early diastolic velocity, **A'**=Peak late diastolic velocity.

**Pancreatic iron and cardiac dimensions and functions**

We divided our patients according to grade of pancreatic iron; group (n=40) with normal pancreatic iron and group (n=20) with pancreatic iron overload. The pancreatic iron overload group showed higher LIC, higher end systolic pulmonary artery pressure (ESPAP) and lower tricuspid annulus peak early diastolic velocity compared to the group with normal pancreatic iron (Table 3).

Pancreatic T2\* correlated positively with peak late diastolic velocity at septal mitral annulus, peak early diastolic velocity at tricuspid annulus and mitral annular plane systolic excursion (MAPSE). It correlated negatively with main pulmonary artery diameter (MPA) and ESPAP (Table 4).

There was a significant negative correlation between LIC and right ventricular dimension at end diastole (RVDD) as well as the following Tissue Doppler parameters: peak systolic velocity at lateral and septal mitral annulus, peak late diastolic velocity at septal mitral annulus and peak early diastolic velocity at tricuspid annulus (Table 4).

**Discussion**

There is accumulating evidence that pancreatic iron can predict cardiac iron in young children<sup>11</sup>. Because the pancreas takes up non-transferrin bound iron, generating reactive oxygen species

of the heart, but earlier, it can be used as an early and strong marker of prospective risk of cardiac siderosis, with a 100% negative predictive value for cardiac iron accumulation<sup>12</sup>. Unfortunately, we failed to test the predictability of pancreatic T2\* in relation to cardiac T2\* in our study as nearly all of our patients had normal cardiac T2\* and only one patient was cardiac iron loaded. In spite of the extensive involvement of the liver and pancreas among our patients, almost absence of cardiac iron loading (n=1) was striking. Several factors affect the transport, storage and removal of iron in the different organs in iron overload conditions leading to the heterogenous distribution of storage iron in each organ measured by MRI T2\*<sup>13</sup>. Genetic background of thalassemic patients in Egypt might be implicated for the low prevalence of cardiac iron loading in our population in spite of very high serum ferritin and high LIC<sup>14</sup>. In another study in Alexandria University performed on thalassemic patients, only 8.7% of cases were cardiac iron loaded<sup>15</sup>. Similarly in SCD patients, Elalfy *et al.* found that cardiac siderosis was absent in transfusion dependant SCD patients with minimal or no pancreatic and moderate to severe hepatic iron loading<sup>16</sup>.

Our results disagree with a study carried out on 131 βTM patients that reported increased cardiac iron in almost one third of patients and increased pancreatic iron in more than 70% of patients with good correlation between pancreatic and cardiac iron (r2= 0.52),

**Table 3. Comparison of hepatic and cardiac iron and cardiac functions in relation to pancreatic iron.**

Mean ± SD (range)	Normal (T2* >11.4) (n=40)	Mild (T2* 3.8- 11.4 ms) (n=20)	P value
LIC	4.06 ± 2.03 (0.6 - 7.13)	5.98 ± 3.17 (0.9 - 11.7)	0.032*
MIC	0.67 ± 0.26 (0.16 - 1.9)	0.72 ± 0.24 (0.13 - 1.12)	0.140
FS	41.35 ± 7.51 (30-55)	39.9 ± 4.67 (30-44)	0.535
EF	71.2 ± 8.08 (58-83)	70.35 ± 5.76 (58-75)	0.478
ESPAP	29.63 ± 8.79 (18-44)	33.4 ± 6.64 (24-44)	0.046*
E' (Lateral mitral annulus)	0.17 ± 0.04 (0.11 - 0.28)	0.18 ± 0.04 (0.12 - 0.28)	0.713
S' (Lateral mitral annulus)	0.1 ± 0.02 (0.05 - 0.14)	0.09 ± 0.02 (0.05 - 0.11)	0.147
A' (Lateral mitral annulus)	0.11 ± 0.06 (0.04 - 0.22)	0.09 ± 0.06 (0.04 - 0.22)	0.285
E' (Septal mitral annulus)	0.15 ± 0.02 (0.08 - 0.17)	0.16 ± 0.03 (0.08 - 0.19)	0.103
S' (Septal mitral annulus)	0.09 ± 0.02 (0.04 - 0.13)	0.08 ± 0.02 (0.04 - 0.12)	0.816
A' (Septal mitral annulus)	0.09 ± 0.05 (0.03 - 0.18)	0.07 ± 0.02 (0.03 - 0.11)	0.425
E' (Tricuspid annulus)	0.18 ± 0.06 (0.06 - 0.28)	0.14 ± 0.04 (0.06 - 0.21)	0.020*
S' (Tricuspid annulus)	0.14 ± 0.05 (0.04 - 0.21)	0.13 ± 0.03 (0.04 - 0.16)	0.400
A' (Tricuspid annulus)	0.12 ± 0.05 (0.03 - 0.19)	0.12 ± 0.05 (0.03 - 0.19)	0.994

\*Statistically significant, LIC=Liver iron concentration, MIC=Myocardial iron concentration, FS=Fractional shortening, EF=Ejection fraction, ESPAP=End systolic pulmonary artery pressure, S'=Peak systolic velocity, E'=Peak early diastolic velocity, A'=Peak late diastolic velocity.

**Table 4. Correlations of pancreatic T2\*, liver iron concentration and ferritin with echocardiographic and tissue doppler variables.**

	Pancreatic T2*		LIC		Serum ferritin	
	R	P	R	P	R	P
LVEDD (mm)	0.195	0.136	-0.130	0.322	-0.053	0.690
LVESD (mm)	-0.082	0.534	0.113	0.391	-0.029	0.826
FS	0.201	0.123	-0.135	0.305	0.078	0.554
EF	0.243	0.062	-0.152	0.245	0.075	0.569
RVDd (mm)	0.160	0.222	-0.268	0.038	-0.208	0.112
LA/Ao	-0.049	0.710	0.088	0.505	0.008	0.953
MPA (mm)	-0.259	0.046	-0.102	0.438	-0.056	0.669
ESPAP	-0.343	0.007	0.168	0.200	0.182	0.163
E' (Lateral mitral annulus)	0.054	0.680	-0.217	0.095	-0.038	0.772
S' (Lateral mitral annulus)	0.224	0.085	-0.313	0.015	-0.149	0.257
A' (Lateral mitral annulus)	0.167	0.203	-0.168	0.198	-0.066	0.617
E' (Septal mitral annulus)	-0.197	0.131	-0.007	0.959	0.128	0.328
S' (Septal)	0.008	0.953	-0.299	0.020	-0.053	0.688
A' (Septal)	0.269	0.038	-0.423	0.001	-0.201	0.124
E' (Tricuspid annulus)	0.430	0.001	-0.335	0.009	-0.184	0.158
S' (Tricuspid annulus)	0.203	0.120	-0.229	0.079	-0.023	0.862
A' (Tricuspid annulus)	0.012	0.928	-0.087	0.509	0.061	0.643
TAPSE	0.236	0.069	-0.082	0.536	-0.042	0.748
MAPSE	0.326	0.011	0.049	0.712	0.106	0.420
Mitral E/A	-0.172	0.189	0.189	0.149	0.142	0.278

**LVEDD**=Left ventricular end diastolic diameter, **LVESD**=Left ventricular end systolic diameter, **FS**=Fractional shortening, **EF**= Ejection fraction, **RVDd**=Right ventricular dimension at end diastole, **LA/Ao**=Ratio of the left atrial dimension to the aortic annulus dimension, **MPA**=Main pulmonary artery, **ESPAP**=End systolic pulmonary artery pressure, **S'**=Peak systolic velocity, **E'**=Peak early diastolic velocity, **A'**=Peak late diastolic velocity, **TAPSE**= Tricuspid annular plain systolic excursion, **MAPSE**=Mitral annular plane systolic excursion, **Mitral E/A**=Ratio of the peak velocity of early diastolic transmitral flow to the peak velocity of the late diastolic transmitral flow, **R**= Spearman correlation coefficient.

with the pancreas loading a decade earlier than the heart<sup>11</sup>. This difference might be explained by the smaller sample size, the design of our study, as well as the younger age group of our patients.

Despite the absence of cardiac iron deposition, there was significant difference between cases and controls ( $p < 0.0001$ ) in diastolic indices of LV (Trans-mitral E/A ratio) and mitral E/A ratio  $> 2$  was found in 30% indicating diastolic dysfunction of restrictive pattern. None of our patients had diastolic dysfunction of impaired relaxation pattern.

The diagnosis of subclinical LV systolic dysfunction can be detected by assessing MAPSE. MAPSE was significantly reduced in patients with chronic heart failure, with a good correlation between MAPSE and EF<sup>17-19</sup>. Among our patients the mean MAPSE was comparable between SCD and controls and was higher in  $\beta$ TM patients ( $p = 0.019$ ) when compared to SCD and controls. This indicates an absence of subclinical LV systolic dysfunction in our studied patients.

Up to one third of our patients had ESPAP  $\geq 35$  mmHg. Moreover, both  $\beta$ TM and SCD groups had significantly higher ESPAP than

controls ( $p < 0.0001$ ). At the time of enrollment 66.7% patients had been splenectomized, also  $\beta$ TM patients had a higher platelet count; both factors could contribute to the higher ESPAP in thalassemia patients. This was in agreement with previous studies that reported splenectomy as one of the main risk factors of cardiac disease in such a group of patients<sup>20,21</sup>.

Comparing the myocardial velocity measurements of cases with controls; there were significant differences in late diastolic ( $A'$ ) and systolic myocardial velocities ( $S'$ ) at the basal mitral annulus of the lateral and septal walls ( $p < 0.0001$ ,  $p = 0.005$ ,  $p = 0.031$  and  $p = 0.004$  respectively) being higher in patients than controls. Also peak systolic velocity ( $S'$ ) at the tricuspid annulus of patients was significantly higher than controls. These findings may be due to the chronic anemia and high cardiac output, which dominate the picture in children unlike other studies that reported that tissue Doppler systolic velocity was significantly lower in the  $\beta$ TM group compared to controls<sup>22</sup>.

Minimal preliminary data have postulated a correlation between pancreatic iron overload and cardiac function in  $\beta$ TM and SCD patients. Our data revealed that pancreatic T2\* correlated positively with peak late diastolic velocity at septal mitral annulus ( $r = 0.269$ ,  $p = 0.038$ ) and peak early diastolic velocity at tricuspid annulus ( $r = 0.430$ ,  $p = 0.001$ ); which means that pancreatic iron overloaded patients had some degree of left and right ventricular diastolic dysfunction respectively, though not yet cardiac loaded. Also patients with pancreatic iron overload had a higher ESPAP compared to those with normal pancreatic T2\* ( $p = 0.046$ ), pancreatic T2\* showed a weak negative correlation with ESPAP ( $r = -0.343$ ,  $p = 0.007$ ) and with main pulmonary artery diameter (MPA) ( $r = -0.259$ ,  $p = 0.046$ ). This means that pancreatic iron load might serve as a good indicator of the risk of developing pulmonary hypertension in  $\beta$ TM and SCD patients even before frank cardiac iron loading and before appearance of cardiac

symptoms as well. Searching the literature, similar correlations between pancreatic T2\* and the development of pulmonary hypertension and diastolic dysfunction could not yet be found. But Pepe *et al.*, in their study on a large cohort of  $\beta$ TM patients, reported that pancreatic iron was correlated to the LV EF, but not to the RV EF<sup>23</sup>.

## Conclusion

Multi-transfused SCD and  $\beta$ TM patients with iron overload showed more iron deposition in the liver, followed by the pancreas with relative sparing of the heart. Assessment of pancreatic T2\* in multi-transfused children and young adults with SCD and  $\beta$ TM can predict myocardial dysfunction detected by Tissue Doppler Imaging in the absence of abnormal indices of global ventricular dysfunction or even the appearance of symptoms and signs of overt heart failure. In fact, we recommend that pancreatic T2\* should be considered as an additional tool to LIC and cardiac T2\* for evaluation and monitoring of young children with  $\beta$ TM and SCD at risk of iron overload. We also recommend that Tissue Doppler echocardiography should be applied in cardiac assessment among patients with chronic hemolytic anemia and should be performed at regular intervals.

## Data availability

### Underlying data

Open Science Framework: Iron overload parameters and early detection of cardiac disease among Egyptian children and young adults with  $\beta$ -thalassaemia major and sickle cell disease: a cross-sectional study, <https://doi.org/10.17605/OSF.IO/58Q3D><sup>24</sup>.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](https://creativecommons.org/licenses/by/4.0/) (CC0 1.0 Public domain dedication).

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# Open Peer Review

Current Peer Review Status:  

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## Version 2

Reviewer Report 06 July 2021

<https://doi.org/10.5256/f1000research.56428.r86937>

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**Hadi Darvishi-Khezri** 

Thalassemia Research Center (TRC), Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran

I have checked the authors' answers and their revisions on the manuscript. The changes and revisions are acceptable in my view.

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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## Version 1

Reviewer Report 20 October 2020

<https://doi.org/10.5256/f1000research.28631.r72131>

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**Hadi Darvishi-Khezri** 

Thalassemia Research Center (TRC), Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran

The article has been reviewed. The study meticulously investigated pancreatic, cardiac and liver iron loading, as well as cardiac dysfunctions among transfusion-dependent  $\beta$ -thalassaemia and sickle cell patients. The researchers tried to reveal the correlation between pancreatic iron loading

with cardiac and liver iron siderosis and also cardiac dysfunction.  
Although the results of study are intriguing, several flaws still remain in the paper.

**Title**

- The title of article is not completely matched with the aim of study.
- The term of cardiac disease used in the title is rather wide. It would be better that more specific term would be chosen for the title of study.

**Abstract**

- The first sentence of the result and method in the Abstract is similar, and a repetition as well (40  $\beta$ TM and 20 transfusion-dependent SCD patients).
- The last sentence in the Abstract part reflects the results of the relationship between pancreatic T2\* values and cardiac iron loading, which is not present in the aim of the study.
- The results of cardiac function were not reflected as part of results in the Abstract.
- It would be better the correlation coefficients (r) in the Abstract would be reported.
- The study did not assess the prediction of cardiac dysfunctions by pancreatic T2\* values. So, a more appropriate substitutional sentence for the conclusion is "There was a relationship between pancreatic iron siderosis with cardiac dysfunction in these patients".

**Introduction**

- The authors stated that the aim of the study is to investigate 1. Cardiac function 2. Cardiac iron loading 3. Their relation to pancreatic iron loading in patients with  $\beta$ -thalassemia major and sickle cell disease (mentioned in the Abstract, Introduction and Discussion sections). However, it seems that the study was established to assess the relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions and liver and cardiac iron siderosis, not a prediction analyses.
- The last sentence in the first paragraph of the Introduction section is vague.

**Method**

- The logic for calculating sample size is missed in this study. The calculation of sample size or a power analysis is necessary.
- Whether the healthy controls has been matched based on age and sex or only age? The first sentence of the Results section in the Abstract part and the main text of the article is different.
- Usually serum ferritin levels of greater than 2000 ng/mL is considered as iron overload in transfusion dependent thalassemia [1]. Hyperferritinemia in non-transfusion dependent thalassemia is a serum ferritin higher than 800 ng/mL [2].

**Results**

- The number (%) of myocardial dysfunctions (systolic and diastolic), pancreatic, cardiac and liver iron siderosis were not clearly reported in the article.
- The authors could have used odds ratio to show the relationship between pancreatic T2\* values with cardiac dysfunction, as well as the strength of the relationship.

- The categorization of patients based on LIC should have been placed in the Method section.
- In the second paragraph, the results related to the prediction of liver siderosis by pancreatic T2\* values is not reflected in the aim of study.
- Figure 2 is not so meaningful.
- Based on the title of Table 3, LIC reported in Table 3 does not belongs to cardiac function.
- I expected to see the status of cardiac and liver MRIs according to pancreatic iron siderosis.
- The majority of correlations between pancreatic T2\*, LIC and serum ferritin with cardiac indices measured by trans thoracic and tissue Doppler echocardiography were weak (correlation coefficient < 0.4). The correlation of LIC and peak late diastolic (A') was detected as a moderate strength of relationship (r = 0.423). The intensity of correlation between pancreatic T2\* with E' was also moderate (r = 0.43).

### Discussion

- The aim of the study should have been mentioned at the end of the Introduction part instead of at the beginning of the Discussion section.
- There is a disparate concept in the paper about the time of pancreatic and cardiac iron loading. In the Abstract it is written: "There is accumulating evidence that pancreatic iron can predict cardiac iron in young children because the pancreas loads earlier than the heart". Conversely, in the second paragraph of the Discussion part it is written: "Cardiac iron overload occurs earlier than pancreatic iron overload, therefore pancreatic iron can predict cardiac iron in young children".
- Wording and writing in the Discussion part is similar to the Results section. To some extent, the Discussion part is the repetition of the results section. Discussion should be the interpretation of the results and a comparison with other studies.
- There have been some limitations in this study, which is absent in the paper. The population of the study is heterogeneous, comprising with  $\beta$ -thalassemia major and sickle cell disease. As you can see, the difference of pancreatic T2\* values between two groups ( $\beta$ TM and SCD patients) shown in Table 1 is significant. In addition, I expected to see several recommendations to make a contribution to set up future studies.

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**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Thalassemia, Clinical Science, Critical Care

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 23 Apr 2021

**yasmeen selim**, Faculty of medicine, Cairo, Egypt

**Title**

**The title of article is not completely matched with the aim of study**

You are right dear sir/I am going to modify the title

- **The term of cardiac disease used in the title is rather wide. It would be better that more specific term would be chosen for the title of study**

I am going to change the term cardiac disease to a more specific term

**Abstract**

- **The first sentence of the result and method in the Abstract is similar, and a repetition as well (40  $\beta$ TM and 20 transfusion-dependent SCD patients)**

I am going to change this sentence

- **The last sentence in the Abstract part reflects the results of the relationship between pancreatic T2\* values and cardiac iron loading, which is not present in the aim of the study**

The aim of our study was to investigate cardiac function and cardiac iron and their relation to pancreatic iron among patients with  $\beta$ -thalassaemia major ( $\beta$ TM) and sickle cell disease (SCD), So the last sentence in the Abstract part that reflects the results of the relationship between pancreatic T2\* values and cardiac iron loading is actually mentioned in the aim of the study

- **The results of cardiac function were not reflected as part of results in the**

**Abstract**

The results of cardiac function were not reflected as part of results in the Abstract as we were restricted by the number of word count of the abstract so we only included the positive correlations with pancreatic T2

- **It would be better the correlation coefficients (r) in the Abstract would be reported**

I will add the r value

- **The study did not assess the prediction of cardiac dysfunctions by pancreatic T2\* values. So, a more appropriate substitutional sentence for the conclusion is "There was a relationship between pancreatic iron siderosis with cardiac dysfunction in these patients"**

I will change this sentence in the conclusion

**Introduction**

- **The authors stated that the aim of the study is to investigate 1. Cardiac function 2. Cardiac iron loading 3. Their relation to pancreatic iron loading in patients with  $\beta$ -thalassemia major and sickle cell disease (mentioned in the Abstract, Introduction and Discussion sections). However, it seems that the study was established to assess the relationships between pancreatic T2\* values and pancreatic iron loading with cardiac dysfunctions and liver and cardiac iron siderosis, not a prediction analyses.**

I am going to edit this part

- **The last sentence in the first paragraph of the Introduction section is vague**

I am going to replace the last sentence in the first paragraph of the Introduction by a more understandable one

**Methods**

- **Whether the healthy controls has been matched based on age and sex or only age? The first sentence of the Results section in the Abstract part and the main text of the article is different**

Healthy controls were both age and sex matched, It is just a typing error I will fix it

- **Usually serum ferritin levels of greater than 2000 ng/mL is considered as iron overload in transfusion dependent thalassemia [1]. Hyperferritinemia in non-transfusion dependent thalassemia is a serum ferritin higher than 800 ng/mL [2]**

The estimation of serum ferritin levels is the most commonly employed test to evaluate iron overload in Beta Thalassemia Major. A target ferritin of approximately 1000 ng/ml is generally recommended standard practice in thalassaemia major (TIF Guidelines, 2000) and other forms of iron overload resulting from blood transfusion. When the

serum ferritin level reaches 1000 ng/ml (usually after 10<sup>th</sup> to 12<sup>th</sup> transfusion), it is generally taken as the point to initiate iron chelation therapy.

**Results**

- **The number (%) of myocardial dysfunctions (systolic and diastolic), pancreatic, cardiac and liver iron siderosis were not clearly reported in the article**

The Hepatic, Cardiac and pancreatic iron loading data are illustrate din table 1 and myocardial dysfunction data are illustrated in the third paragraph in results and table

2

- **The categorization of patients based on LIC should have been placed in the Method section**

Categorization of patients based on LIC will be added in methods section

- **In the second paragraph, the results related to the prediction of liver siderosis by pancreatic T2\* values is not reflected in the aim of study**

The results related to the prediction of liver siderosis by pancreatic T2\* values is not reflected in the aim of study as this was a secondary outcome not our primary one

- **Figure 2 is not so meaningful**

Figure 2 is based on the secondary outcome that we found

- **Based on the title of Table 3, LIC reported in Table 3 does not belongs to cardiac function**

I will change the title of table 3

- **The majority of correlations between pancreatic T2\*, LIC and serum ferritin with cardiac indices measured by trans thoracic and tissue Doppler echocardiography were weak (correlation coefficient < 0.4). The correlation of LIC and peak late diastolic (A') was detected as a moderate strength of relationship (r = 0.423). The intensity of correlation between pancreatic T2\* with E' was also moderate (r = 0.43)**

Though the correlations are weak but there still exist a correlation and this is actually what we found

### **Discussion**

- **The aim of the study should have been mentioned at the end of the Introduction part instead of at the beginning of the Discussion section**

I will remove this part

- **There is a disparate concept in the paper about the time of pancreatic and cardiac iron loading. In the Abstract it is written: "There is accumulating evidence that pancreatic iron can predict cardiac iron in young children because the pancreas loads earlier than the heart". Conversely, in the second paragraph of the Discussion part it is written: "Cardiac iron overload occurs earlier than pancreatic iron overload, therefore pancreatic iron can predict cardiac iron in young children"**

I am going to edit this part regarding Cardiac iron overload occurs earlier than pancreatic iron overload, therefore pancreatic iron can predict cardiac iron in young children as it is really contradictory

- **There have been some limitations in this study, which is absent in the paper. The population of the study is heterogeneous, comprising with  $\beta$ -thalassemia major and sickle cell disease. As you can see, the difference of pancreatic T2\***

**values between two groups (βTM and SCD patients) shown in Table 1 is significant. In addition, I expected to see several recommendations to make a contribution to set up future studies**

I will add some recommendations as suggested

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 21 September 2020

<https://doi.org/10.5256/f1000research.28631.r71231>

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**Emanuele Angelucci** 

Department of Oncology and Hematology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

I have reviewed the document from my Egyptian colleagues with great interest. This paper is well written and addresses an important topic which is the clinical damage by iron overload and the efficacy of iron chelation therapy in a population of young children in the southern Mediterranean area.

The article is clear and of relevance also because the population described is rarely seen in industrialized countries and consequently today rarely described in international medical journals.

Furthermore, modern diagnostic technology is applied in a young hemoglobinopathy population suffering from severe iron-overloaded (probably inadequately chelated). Of relevance the conclusions are supported by an adequate (# 60) and well-studied age-matched control group.

Although the main goal is, as expected, partially not achieved (correlation between pancreatic-hepatic iron with cardiac iron), there are several important conclusions from this article: Pancreatic iron concentration and liver iron concentration are good predictors of early cardiac function impairment.

Very important: Cardiac function begins to deteriorate long before cardiac iron deposition is manifest by T2 \* MRI even in a population of young children (mean age 13 years): this observation once again underlines the need for a regular (even intensive) iron chelation since initial stages of transfusion dependence.

Correctly the authors use liver iron concentration as the standard for iron overload throughout the body<sup>1</sup>.

To improve paper readability, I suggest the following:

Please clarify the definition of transfusion dependence (methods first paragraph).

Few data are reported twice (methods and results; results and discussion). This is not necessary. The technical details of MRI and cardiac ultrasound are not needed. They can simply be referenced.

Please be consistent with the definition of liver iron concentration (page 3: liver and pancreas T2 \* versus second paragraph results). Liver iron concentration <2 mg / g dw is normal, liver iron concentration between 2 and 7 mg / g dw is mild overload.

Figure 1 is unnecessary and can be deleted.

Likewise, Tables 1 and 4 can be omitted.

Table 5: missing caption.

The discussion can be shortened.

I don't understand reference no. 24.

Include demographic details of the control population (age, gender, etc.).

As a further question: Did the authors observe any difference between thalassemia and sickle cell disease?

### References

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**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Iron overload and iron toxicity. Hemopoietic cell transplantation.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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