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Acta Haematologica Polonica

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Authors: Haleh Bozorgi, Shahdad Khosropanah, Sezaneh Haghpanah, Omid Reza Zekavat

DOI: 10.5603/ahp.95958

Article type: Original research article

Submitted: 2023-06-11

Accepted: 2023-08-03

Published online: 2023-11-22

A plenary survey on the Incidence of cardiac complications amongst transfusion-dependent thalassemia patients

Haleh Bozorgi[1], Shahdad Khosropanah[2], Sezaneh Haghpanah[1], Omid Reza Zekavat[*]

[1]Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Department of Cardiology, Shiraz University of Medical Sciences, Shiraz, Iran

*Address for correspondence: Omid Reza Zekavat, Hematology Research Center, Shiraz University of Medical Sciences, Nemazee Hospital, Shiraz, 71937-1135, Iran, phone +98 71 36 122 263, e-mail: ozekavat@gmail.com

Abstract

Introduction: Cardiac complications are the leading cause of mortality amongst transfusion-dependent thalassemia (TDT) patients. The multifactorial etiology of cardiac disorders has made their management quite challenging. Therefore, in addition to evaluating the incidence of heart failure (HF) and pulmonary hypertension (PHT), the associated factors were assessed amongst 737 TDT patients, aiming to achieve a plenary perspective of their cardiac disorders and relative factors.

Material and methods: In this cross-sectional, we evaluated the incidence of HF and PHT amongst 737 TDT patients while considering imperative factors such as endocrinopathies, iron status, and serum vitamin D level.

Results: Incidence of total heart failure and pulmonary hypertension were estimated at 12.3% amongst participants, however, the rate of cardiac iron overload was about 40%. Splenectomy, serum vitamin D, low bone mass, age, gender, hypoparathyroidism, hypogonadism, and diabetes were significantly impairing the cardiac function of our patients. The latter results were concluded by univariate analysis and only the frequency of blood transfusion proved to have a risk effect on left ventricle ejection fraction.

Conclusions: Cardiac iron overload has the highest impact on the incidence of cardiac disorders amongst TDT patients. Even though the significant statistical association between studied

disorders and iron chelation regimen, endocrinopathies, splenectomy, serum vitamin D, and total body iron status were not observed, however about clinical practice, their effect could not be ignored and require further studies to achieve efficient management of thalassemia patients with cardiac disorders.
Keywords: cardiac complications, heart failure, pulmonary hypertension, thalassemia

Introduction

Nowadays, transfusion-dependent Beta-thalassemia patients (TDT), seek more medical attention due to increased survival rates and disease-related complications for a better quality of life [1]. Cardiac complications, one of the most studied subjects amongst TDT patients still counts as a leading cause of mortality. Diastolic dysfunction, tricuspid regurgitation, pulmonary hypertension, heart failure, and arrhythmias are the most recorded manifestations of cardiac disorders [2]. In TDT like many other disorders, such as osteoporosis and endocrinopathies, cardiac complications are triggered by iron overload as a result of frequent blood transfusions [3]. Despite iron chelation therapy and transfusion to improve anemia, cardiac complications still develop [4]. HF is described as impaired ventricle function that results in decreased cardiac output, therefore measuring left ventricle ejection fraction (LVEF) is considered an appropriate parameter to detect heart failure (HF) [5, 6]. pulmonary hypertension (PHT), as another common cardiac complication of TDT, is a hemodynamic condition and is diagnosed when pulmonary artery pressure (PAP) is more than 20 mm Hg. The gold measurement method of the latter factor is through right heart catheterization. However, the method is quite invasive, and currently, transthoracic echocardiography is a favorable method to detect PTH probability. As a result, when PHT is suspected via echocardiography further investigation like cardiac magnetic resonance (CMR) could be helpful in definite diagnosis [7]. The multifactorial nature of aforementioned cardiac disorders necessities evaluation of possible associated factors. As such, iron chelation regimen, splenectomy, and bone mass are other associated factors that are still assessed in cardiac complications in addition to gender, age, amount of transfusion, vitamin D serum level, hemoglobin, and many others. Measuring LVEF and assessing PH are precise factors for monitoring cardiac function. Assessment of cardiac disorders is advised via annual

electrocardiogram, echocardiography, and T2* CMR amongst thalassemia patients to provide better management [8]. CMR even provides predictive assessment for cardiac complications [9-13]. Herein, we compiled a review concerning HF and possible PHT by assessing 737 TDT patients. Alongside reporting their incidence, we focused on possible associated factors in addition to finding a possible correlation between low bone mass and cardiac complication, to determine their exact role to provide more accurate guidelines for assessing cardiac complications.

Material and methods

Patients

Seven hundred seventy-eight transfusion-dependent thalassemia patients from the Dastgheib comprehensive thalassemia center were enrolled in this historical cohort from September 2021 to August 2022.

Beta thalassemia was confirmed via hemoglobin electrophoresis and patients were transfusion dependent to postulate pre-transfusion hemoglobin above 9 g/dL, and those older than 15 years old with regular blood transfusion were included. Patients with poor cardiology follow-up, bone marrow-transplanted patients, those with active hepatitis B or C, human immunodeficiency virus (HIV) infection, liver cirrhosis, congenital cardiac complications, and incomplete medical record were excluded. In total, 41 patients were excluded and 737 participants remained in the study. Patients were on different iron chelation therapy (ICT) based on total body iron and cardiac status. According to 4 groups of ICT regimens that we determined for our patients, the classifications are as follows Group 1, patients who used DFO (**Desferal®, Novartis**) with the dosage of 30–50 mg/kg daily 5–7 nights/week via subcutaneous infusion pump. Group 2 used deferiprone (DFP) (**Avicenna pharmaceutical**) tablets with a dosage of 75 mg/kg daily. Group 3 (n = 71) took deferasirox (DFX) (**Exjade®, Novartis**) oral chelator with the dosage of 20–40 mg/kg daily. Group 4 was prescribed a combination regimen of either DFP and DFO in the same mentioned dosages, or a combination of DFO and DFX. Patients who were suffering from low bone mass or vitamin D deficiency were prescribed vitamin D 50,000 IU weekly supplements for 6 to 8 weeks. Those with hypoparathyroidism were on calcitriol (0.25–2.0 μg/day). Levothyroxine was prescribed for TDT patients with hypothyroidism by an endocrinologist during their annual visit. Furthermore, the patients with low bone mass were on

either alendronate (**Fosomax®, Merck & Co., Inc**) 70 mg weekly or zoledronic acid (**Zometa®, Novartis**) 4 mg intravenous infusion over 45 min twice a year.

Included data were splenectomy status, blood transfusion frequency, and endocrine status.

Splenectomy was considered when symptomatic splenomegaly, increased amount of blood transfusion, impaired growth status, and thrombocytopenia became present.

Written informed consent was obtained from each individual or their legal guardians who accepted to participate in this study. The study was approved by the local Ethics Committee.

Cardiac assessment

The annual echocardiography was done by a single expert cardiologist, determining LVEF and PAP. Heart failure was considered if LVEF was below 50%. In addition, T2* magnetic resonance imaging (MRI) of the liver and heart (SEIMENS, Germany, Avanta, 1.5 Tesla) was done for all patients, and iron loading was categorized as follows: cardiac T2*MRI; normal: >20, mild:14–20, moderate:10–14, severe <10.

Biochemical laboratory data

Based on our center's routine protocol, 5 ml of venous blood was taken after 8 hours of fasting from each patient by a technician. Serum 25-OH vitamin D and ferritin levels were measured using electrochemiluminescence methods with Cobas 411 (Roche, Germany). Serum ferritin level was measured every 3 months and hemoglobin level was assessed before and post blood transfusions. The last three documented hemoglobin and ferritin were considered in data analysis.

Bone mineral densitometry

Lumbar spine (L1–L4) and right femoral neck bone mineral density (BMD) were measured using the hologic system dual energy X-ray absorptiometry (DXA) (Discovery QDR, USA). The data of the Hologic system DXA, which was obtained from the US Centers for Disease Control's 'National Health and Nutrition Examination Survey' (NHANES), were used to interpret BMD Z-scores and normative data. Low bone mass (LBM) was diagnosed based on the definition of the International Society for Clinical Densitometry (ISCD) of a Z-score of −2 or lower as 'below the

expected range for age' [14]. Based on the measurements of 15 patients, the coefficient of variation was 0.5% for the lumbar spine and the femoral neck in our center.

Associated factors

A form was filled out by an expert by asking the patients subjectively to classify physical activity into three groups suggested by the American College of Sports Medicine: no physical activity, 1 hour of physical activity less than three times a week, and at least 1 hour of physical activity more than three times a week. Body mass index (BMI) was measured and calculated by a trained health professional. Height was measured by a standard wall-mounted meter and rounded to the nearest 0.5 cm. Weight was assessed via a standard scale (Seca, Germany), while the patients were wearing light cloth with no shoes. BMI was calculated using the standard formula, BMI (kg/m^2) = weight (kg)/[height (m^2)], and classified into four groups: underweight (<18.5), healthy (18.5–24.9), overweight (25.0–29.9), and obese (>30) [15, 16].

All patients were prescribed to take calcium 500 mg and vitamin D 400 IU supplements, daily. Patients with vitamin D deficiency received weekly 50,000 unit vitamin D pearl for 8 weeks. As for liver iron load classification was: normal (>6.3), mild (2.8–6.3), moderate (1.4–2.7), and severe (<1.4). serum ferritin level was classified as mild (serum ferritin < 1000 ng/mL), moderate (serum ferritin 1000–2500 ng/mL), and severe (serum ferritin >2500 ng/mL) [17].

Patients were classified into three groups concerning their SERUM 25(OH) vitamin D level: sufficient (>50 nmol/L), insufficient (30–50 nmol/L), and deficient (<30 nmol/L) according to Institute of Medicine (IOM) [18].

Statistical analysis

Data analysis was performed by SPSS software version 17 (SPSS Inc., Chicago IL, USA). Descriptive results are presented as mean, standard deviation, frequency, and percentage. Correlation between quantitative variables was done by the Pearson Correlation test. Comparison of quantitative variables was done by student *t*-test between two groups and by ANOVA test among different groups. Qualitative variables were compared by Chi-square test among different groups. Variables with p value less than 0.2 in univariate analysis were entered into multivariate analysis. Multiple logistic regression analysis was done by Enter method. P-values less than 0.05 were considered to be statistically significant.

Results

The cardiac status of 737 TDT patients with a mean age of 28.02 ± 9.36 was assessed during a year of study. Gender distribution was almost equal (51% female) and patients' hemoglobin levels were 9.37 ± 1.17. The general characteristics of the studied patients are summarized in Table I.

Table I. General characteristics of studied transfusion-dependent thalassemia patients

Age (y) (mean ± SD)	28.02 ± 9.36
Gender n [%]	Female 376 (51.01) Male 361 (48.99)
Splenectomy, n [%]	276 (37.4)
Splenectomized period [y] (mean ± SD)	19.09 ± 10.18
Blood transfusion/year	19.1 ± 6.66
Low bone mass [%]	59.8
Heart failure	38(5.2)
Last 3 hemoglobin [g/dl] (mean ± SD)	9.7±1.04
Last 3 serum ferritin mean level [ng/mL] (mean ± SD)	3,027.21 ± 2,690.86
Mild [%]	26.7
Moderate [%]	31.6
Severe [%]	41.7
Physical activity [%]	Group 1 (16.7) Group 2 (48.8) Group 3 (34.5)
Bisphosphonate therapy, n [%]	Alendronate 154 (20.9) Zoledronic acid 128 (17.4)
Cardiac complication, n [%]	91 (12.3)
Diabetes, n [%]	(81) 10.9
Hypoparathyroidism, n [%]	(67) 9
Hypothyroidism, n [%]	(35) 4.7
PHT, n [%]	(88) 11.9
Heart failure, n [%]	38 (5.2)
LVEF (mean ± SD)	58.89 ± 5.37
Vitamin D (mean ± SD)	27.77 ± 20.68
<50 ng/mL [%]	86.8

>50 ng/mL [%]	13.2
Cardiac T2 MRI (mean ± SD)	23.03 ± 11.06
Classification [%]	Normal 60.1 Mild 14.4 Moderate 9.5 Severe 16
Liver T2 MRI (mean ± SD)	6.58 ± 6.24
Classification [%]	Normal 28.6 Mild 49.5 Moderate 21.7 Severe 0.2

PHT — pulmonary hypertension; LVEF — left ventricular ejection fraction; MRI — magnetic resonance imaging

Heart failure

The univariate analysis determined a significant correlation between EF and LBM (p = 0.033), splenectomy (p = 0.046), liver T2 MRI (p = 0.009), serum vitamin D (p = 0.013), age (p = 0.004), diabetes (p = 0.025), hypoparathyroidism (p <0.001), hypogonadism (p = 0.007), serum ferritin (p = 0.035), and heart T2 MRI (p <0.001) (Table II). Considering the significant correlation between LVEF and heart T2 MRI, most of the concerned associated factors were entered in univariate analysis with heart T2 MRI as well. LVEF (p = 0.002), gender (p = 0.013), splenectomy (p = 0.029), liver T2 MRI, (p = 0.002), mean serum ferritin (p <0.001), LBM (P = 0.014), serum vitamin D level (p = 0.007) and ICT regimen (p = 0.001) were the statistically relevant factors. Male gender and splenectomy had an apposable correlation with cardiac T2 MRI (Table III). Such analysis with aforementioned variants was done based on liver T2 MRI, as another index of iron load, but no significant associations were observed.

Table II. Univariate analysis between left ventricular ejection fraction (LVEF) and associated factors

Parameter	**LVEF ≥50**	**LVEF <50**	**p value**
PHT (mean ± SD)	28.01 ± 7.53	30.69 ± 8.43	0.490

Splenectomized patients, n [%]	37.3% 252	52.6 20	0.046*
Splenectomy duration (mean ± SD)	19.02 ± 10.17	20.40 ± 9.31	0.559
Liver T2 MRI (mean ± SD)	6.69 ± 6.35	4.8 ± 3.73	0.009*
Ferritin (mean ± SD)	3004.93 ± 2698.79	3780 ± 2716.32	0.035*
Hemoglobin (mean ± SD)	9.72 ± 1.03	9.49 ± 1.04	0.200
Low bone mass [%]	59.8	84.2	0.033*
Gender [%] Male/female	44/52.6	56/47.4	0.458
Vitamin D insufficiency [%] <50 ng/mL	12.6/87.4	31.3/68.8	0.032*
Mean of last 3 hemoglobin (mean ± SD)	9.72 ± 1.03	9.49 ± 1.04	0.200
Transfusion number/year (mean ± SD)	19.13 ± 6.61	20.92 ± 6.95	0.106
PAP (mean ± SD)	33.43 ± 25.76	62.52 ± 54.91	0.212
Age (mean ± SD)	28.31 ± 8.79	32.34 ± 7.49	0.004*
Diabetes [%]	15.9	35	0.025*
Hypoparathyroidism [%]	12.4	40	<0.001*
Hypogonadism [%]	44.6	75	0.007*
Hypothyroidism [%]	7.2	10	0.634
BMI [%]			0.914
1	68.8	75	
2	26.9	20	
3	4.1	5	
4	0.2	0	
Physical activity [%]			0.844
1	16.7	15	
2	49.6	45	
3	33.7	49.4	
Heart T2 MRI			<0.001*
Normal	96.6	3.4	
Mild	96.5	3.5	
Moderate	82.5	17.5	
Severe	91.7	5.5	

*Statistically significant; PHT — pulmonary hypertension; SD — standard deviation; MRI — magnetic resonance imaging; PAP — pulmonary artery pressure; BMI — body mass index

Cardiac T2 MRI	**Normal 60.2%**	**Mild 14.45%**	**Moderate 9.51%**	**Severe 16.02%**	**p value**
LVEF	59.46 ± 5.02	59.03 ± 4.93	57.57 ± 5.97	57.45 ± 6.24	0.002*

PAP	27.31 ± 7.09	28.68 ± 6.65	32.06 ± 12.68	27.55 ± 5.94	0.117
Gender [%] Female/male	58.3/41.7	58.1/41.9	45.6/54.4	41.7/58.3	0.013*
Splenectomy [%]	56.6	13.7	8	21.7	0.029*
Splenectomy duration (mean ± SD)	20.6 ± 9.76	17.68 ± 11.03	19.78 ± 9.37	16.22 ± 9.2	0.170
Liver T2 MRI (mean ± SD)	7.95 ± 6.9	5.1 ± 4.79	4.34 ± 2.9	4.1 ± 4.4	0.002*
Mean ferritin (mean ± SD)	2117.72 ± 2088.1	3581 ± 2633.74	3838.47 ± 2959.69	5166.23 ± 2914.01	<0.001*
Low bone mass [%]	57.8	62.3	78.9	74.2	0.014*
Gender [%] male/female	41.7/58.3	41.9/58.1	54.4/45.6	58.3/41.7	0.013*
Vitamin D (mean ± SD)	31.37 ± 23.19	27.17 ± 17.47	22.73 ± 19.08	21.01 ± 15.32	0.007*
Mean hemoglobin (mean ± SD)	9.75 ± 0.96	9.81 ± 0.95	9.7 ± 0.94	9.92 ± 1.08	0.477
Transfusion number/year (mean ± SD)	19.13 ± 7.54	20.29 ± 4.74	20.19 ± 5.05	19.8 ± 4.93	0.368
ICT**					0.001*
1	17.6	16.7	12	11.4	
2	5.9	4.2	0	2.3	
3	37.8	18.8	24	9.1	
4	38.8	60.4	64	77.3	

*Statistically significant; **ICT (iron chelation treatment): 1 — deferoxamine, 2 — deferiprone, 3 — deferasirox; 4 — the combination of deferoxamine + deferiprone; or deferoxamine + deferasirox; LVEF — left ventricle ejection fraction; PAP — pulmonary artery pressure; SD— standard deviation

Pulmonary hypertension

Overall cardiac complications, based on heart failure and pulmonary hypertension were reported at 12.3% with a heart failure rate of 5.2%. It should be kept in mind that there were patients who suffered from both cardiac disorders.

Pulmonary hypertension (PHT), with a prevalence of 11.9%, as another cardiac complication was considered and assessed by analysis of possible associated factors. Splenectomy ($p = 0.006$), the number of transfusions/year (0.029), and physical activity ($p = 0.034$) were significantly related to PHT.

Multiple logistic regression with Enter method was used to determine independent factors associated with cardiac complications. Variables with a P value less than 0.2 in the univariate analysis were entered into the regression model. The only significant covaries appears to be the amount of transfusion per year with LVEF ($p = 0.046$, 95% Odds Ratio = 1.13 CI:1.002-1.28). ICT was also assessed in patients with heart failure and PHT, although results were insignificant, patients on a combination regimen had higher mean LVEF and lower incidence of PHT.

Discussion

In this cross-sectional study, we had a record of 12.3% cardiac complications amongst 737 TDT patients, of which 88 had possible PHT and 38 had suffered from HF. Regarding iron loading, almost half the patients had normal T2 MRI heart, but 40 percent had severe iron overload based on the serum ferritin level. Vitamin D serum level, splenectomy, serum ferritin, age, diabetes, hypoparathyroidism, and hypogonadism had proven to statistically play a significant role. However, the regression analysis test did not confirm any of the latter factors to be significantly related.

Assessing the cardiac status of TDT patients is a continuous and mandatory matter, considering it is a leading of mortality. Koohi et al. [2] reported a prevalence of cardiac complications at 42% with a cardiac iron overload of 25% amongst 26,893 beta-thalassemia major patients. We focused on heart failure and pulmonary hypertension as cardiac complications and the prevalence was one-fourth of the aforementioned large meta-analyses, but cardiac iron overload was almost twice the latter study. The difference between the numbers can be simply explained by the difference in the number of studied populations; in addition, we should consider

patients with cardiac iron overload are prone to develop cardiac complications [2]. Based on the region of our patients, several cardiac iron overload patients were in line with reports from Carpenter et al. which highlight the point of the importance of district in this regard [19–21].

The multifactorial nature of TDT patients' cardiac complications is of interest to physicians over the associated factors. Cardiac iron overload is the main proven issue in inducing cardiac complications, which counts as a predictive criterion as well [22]. Of the indices revealing body iron status in TDT patients, we observed cardiac T2 MRI had the most association with relevant factors. We also observed patients with higher cardiac iron load to be mostly combined ICT. The latter point is a result of following T2 MRI as an index of determining suitable ICT; in cardiac complications, combination therapy can provide better cardiac outcomes [23]. The significant correlation between ICT and cardiac T2 MRI ($p = 0.001$) was not observed with the serum ferritin, liver T2 MRI or LVEF. This result could suggest that cardiac T2 MRI could be the most suitable and sensitive index for choosing an ICT regimen. Kwiatkowski et al. [24] provided a survey regarding the iron burden of thalassemia patients with results in line with the current study. On another iron overload-related issue, we reached a significant correlation between the number of transfusions/year and PHT. In line with previous surveys, the result is acceptable that those with more frequent blood transfusions would suffer more from iron overload-related complications [25]. Although insignificant patients with PHT were mostly on combined ICT regimens.

Alongside cardiac T2 MRI and iron burden, splenectomy appeared to play a prominent role in cardiac complications as well. The significant correlation between lower LVEF, and a high rate of PHT and cardiac iron load with splenectomy is another concern regarding the cardiology status of TDT patients. Splenectomy is recommended only under necessary circumstances and in a previous study regarding endocrine disorders we concluded the risk effect of splenectomy in developing or compromising low bone mass and endocrinopathies; now with current results and based on previous and recent studies, we shall mention splenectomy as a serious predisposing factor in the cardiac status of TDT patients [21, 26]. Derchi et al. [27] reported ferritin and splenectomy as serious risks for developing cardiac complications in TDT patients in a study with half of our population. We reached such a conclusion as well but serum ferritin was significantly associated with LVEF and cardiac T2 MRI. Previously in the current center, our colleagues determined that serum ferritin could be an alternative index for

determining iron status if T2 MRI was not available [28]. Based on the results, relying on serum ferritin could provide a preliminary assessment but might lead to missing many associated factors. Hiradfar et al. [29] conducted a study on the relevance of vitamin D serum level and cardiac T2 MRI and followed LVEF changes of their 16 TDT patients following vitamin D treatment and improvement turned out to be significantly related. Subsequently, we analyzed serum vitamin D levels with LVEF and cardiac T2 MRI, proving the significant correlation. Such a result was not obtained through serum ferritin and liver T2 MRI. Vitamin D deficiency impairs the myocardium by increasing serum parathyroid hormone, leading to heart failure. Despite close endocrinology monitoring, only 13.2% of our patients had optimal serum vitamin D levels, which points out patients' compliance and adherence, and reinforces closer watch and follow-up to improve cardiac status; in addition to other vitamin D related endocrinopathies such as low bone mass and hypoparathyroidism. Regarding endocrinopathies, later disorders as well as hypogonadism and diabetes were significantly associated with LVEF. Diabetes is a proven risk factor for cardiology status no matter whether there is an underlying disease or not. But it happens to be a prominent risk factor in the cardiac status of TDT patients as well [30]. The negative correlation between LVEF and endocrinopathies calls for closer and more intensive endocrinopathy management amongst TDT patients with cardiac complications. Since the prevalence of endocrine disorders is more than 80%, according to many surveys [3] it could be quite challenging to provide acceptable management. We determined that LBM was the most prevalent endocrine disorder in TDT patients in our center, and here we found it to adversely affect LVEF. The risk of osteoporosis in cardiovascular disease is established in [31], yet the association of low bone mass and cardiac complications in TDT patients is understudied. The basic etiology of both disorders remains iron overload, but when they developed, LBM can deteriorate the cardiac status of TDT patients. Kyriakou et al. showed that severe cardiac iron status was correlated with low bone mass [32]. Here we determined the correlation with heart failure and emphasize intensive bisphosphonate therapy for patients with both low mass and heart failure. Following the latter correlation, we evaluated the possible association of bisphosphonate therapy and cardiac status which revealed no specific result; however, those who were taking zoledronic acid had more acceptable LVEF so further assessments would provide more accurate results. Like many other TDT-related complications, age and gender were related to cardiac complications. With the increase in age, the LVEF decreased significantly and males

appeared to have more cardiac complications than females, which was previously reported in [33]. Therefore, closer cardiac observation would be advised amongst male TDT patients.

The fact that regression analysis did not provide any significant correlation could be explained by the multifactorial etiology of cardiac complications in TDT patients which calls for more comprehensive and prospective studies. Our study was conducted in a comprehensive thalassemia center on a great number of the population while considering important associated factors which count as prominent strengths. Despite the latter point, we faced noticeable limitations as well such as a lack of data availability on arrhythmias and the fact that the study was retrospective.

A larger multi-center study is highly advised to provide more accurate data while considering more associated factors to deliver management guidelines.

Conclusion

We believe the 18 years of cardiology follow-up has led to lower cardiac complications in our center's patients. But the high rate of iron overload is an alarming fact that through the data analysis was significantly related to the incidence of HF and possible PTH which requires more thorough follow-up on the ICT regimen and patients' compliances. The clinical experience of our hematologist and cardiologist has also implied that managing other associated factors such as endocrine disorders, splenectomy rate, and serum vitamin D level lowers the rate of cardiac disorders and therefore mortality rate.

Acknowledgments

The authors wish to thank Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in editing this manuscript. We also thank Shirin Parand at the Hematology Research Center for preparation of the manuscript.

Authors' contributions

HB is the main author who designed the study and wrote considerable amount of article. SH. khosropanah: helped with editing and preparation of the script and was the cardiologist involved

with our participants. SH she was the main analyst and provided the presented results and edited the script exactingly. OZ participated in designing the study, gathering data and editing the script.

Conflict of interest

All authors declare that they have no conflict of interest.

Financial support

None.

Availability of data and material

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

Patient consent statement

A written consent form was obtained from all patients or their legal guardians.

Ethical statement

The study was approved by the local Ethics Committee of Shiraz University of Medical Sciences.

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