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Plenary survey on incidence of cardiac complications among transfusion-dependent thalassemia patients

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Abstract

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

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

Results: The incidence of total heart failure and pulmonary hypertension were estimated at 12.3% among participants, although the rate of cardiac iron overload was c.40%. Splenectomy, serum vitamin D, low bone mass, age, gender, hypoparathyroidism, hypogonadism, and diabetes significantly impaired the cardiac function of our patients. In univariate analysis, 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 among TDT patients. We observed significant statistical associations between both HF and PHT with iron chelation regimen, endocrinopathies, splenectomy, serum vitamin D, and total body iron status in univariate analysis. Such results were not statistically significant in multiple logistic regression. However, in clinical practice, their effect could not be ignored. Further studies are required to achieve efficient management of thalassemia patients with cardiac disorders.

Key words: cardiac complications, heart failure, pulmonary hypertension, thalassemia

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Introduction

Nowadays, transfusion-dependent beta-thalassemia patients (TDT) need more medical attention due to increased survival rates and more disease-related complications threatening their quality of life [1]. Cardiac complications, one of the most studied subjects among TDT patients, are still a leading cause of mortality. Diastolic dysfunction, tricuspid regurgitation, pulmonary hypertension, heart failure, and arrhythmias are the most commonly recorded cardiac disorders [2]. In TDT, as in 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]. Heart failure (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 HF [5, 6]. Pulmonary hypertension (PHT), 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 standard

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measurement of PHT is via right heart catheterization. However, this method is invasive, and transthoracic echocardiography is a favored method of detecting PHT probability. As a result, when PHT is suspected via echocardiography, further investigation such as cardiac magnetic resonance (CMR) help establish a definite diagnosis [7].

The multifactorial nature of the aforementioned cardiac disorders necessitates the evaluation of possible associated factors. As such, iron chelation regimen, splenectomy, and bone mass are associated factors that are still assessed in cardiac complications in addition to gender, age, amount of transfusion, vitamin D serum level, hemoglobin, and 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* cardiac magnetic resonance (CMR) among thalassemia patients to provide better management [8]. CMR even provides predictive assessment for cardiac complications [9–13].

Below, we have compiled a review concerning HF and possible PHT by assessing 737 TDT patients. As well as reporting their incidence, we have focused on possible associated factors in addition to finding any correlation between low bone mass and cardiac complications, to determine their exact role to provide more accurate guidelines for assessing cardiac complications.

Material and methods

Patients

Seven hundred and seventy-eight transfusion-dependent thalassemia patients from the Dastgheib Comprehensive Thalassemia Center in Iran were enrolled in this historical cohort from September 2021 to August 2022.

Beta thalassemia was confirmed via hemoglobin electrophoresis, and patients were deemed transfusion-dependent if their pre-transfusion hemoglobin level was 9 g/dL. Those aged 16 or over with regular blood transfusions were included. Patients with a poor cardiology follow-up, a bone marrow transplant, those with active hepatitis B or C, human immunodeficiency virus (HIV) infection, liver cirrhosis, congenital cardiac complications, or incomplete medical records were excluded. In total, 41 patients were excluded and 737 participants remained in the study. Patients were on different iron chelation therapies (ICT) based on their total body iron and cardiac status.

We determined four groups of ICT regimens for our patients. The classifications were as follows: Group 1 patients used deferoxamine (DFO) with the dosage of 30–50 mg/kg daily 5–7 nights/week via a subcutaneous infusion pump; Group 2 used deferiprone (DFP) tablets with a dosage of 75 mg/kg daily; Group 3 (n = 71) took deferasirox (DFX) oral chelator with the dosage of 20–40 mg/kg daily; and Group 4 patients were prescribed a combination regimen of either DFP and DFO in the abovementioned 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 6–8 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 70 mg weekly or zoledronic acid in a 4 mg intravenous infusion over 45 minutes twice a year.

We collected data regarding splenectomy status, blood transfusion frequency, and endocrine status.

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

Written informed consent was obtained from each individual, or their legal guardian, to participate in this study. This study was approved by the local Ethics Committee.

Cardiac assessment

An annual echocardiography was done by the same 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 (SIMENS, 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, or 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 three months, and hemoglobin level was assessed before and after blood transfusions. The last three documented hemoglobin and ferritin values were considered in the 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). Data from DXA, which was obtained from the US Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES), was 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 filled out by an expert asked the patients subjectively to classify their physical activity into the three groups suggested by the American College of Sports Medicine: no physical activity, or one hour of physical activity less than three times a week, or at least one 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 patients were wearing light clothing 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), or 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 a weekly 50,000-unit vitamin D pearl for eight weeks. Liver iron load classification was: normal (>6.3), mild (2.8–6.3), moderate (1.4–2.7), or severe (<1.4). Serum ferritin level was classified as mild (serum ferritin <1,000 ng/mL), moderate (serum ferritin 1,000–2,500 ng/mL), or severe (serum ferritin >2,500 ng/ /mL) [17].

Patients were classified into three groups according to their serum 25(OH) vitamin D level: sufficient (>50 nmol/ /L), insufficient (30–50 nmol/L), or deficient (<30 nmol/L) according to the 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 the Enter method. P-values of 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 years was assessed over the course of 12 months 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 set out in Table I.

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

Variables	Value
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 levels [g/dL] (mean ± SD)	9.7 ± 1.04
Last 3 serum ferritin mean levels [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 complications, 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

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

Pulmonary hypertension

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

Pulmonary hypertension (PHT), with a prevalence of 11.9%, was considered and assessed as another cardiac complication 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 the Enter method was used to determine independent factors associated with cardiac complications. Variables with a P value of less than 0.2 in univariate analysis were entered into the regression model. The only significant covariate appears to be the number of transfusions per year with LVEF [p = 0.046, 95% odds ratio = 1.13 confidence interval (CI): 1.002–1.28]. ICT was also assessed in patients with heart failure and PHT, although the results were insignificant, and patients on a combination regimen had higher mean LVEF and lower incidence of PHT.

Discussion

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

Assessing the cardiac status of TDT patients is a continuous and mandatory undertaking, considering that it is a leading cause of mortality. Koohi et al. [2] reported a prevalence of cardiac complications at 42% with a cardiac iron overload of 25% among 26,893 beta-thalassemia major patients.

We focused on heart failure and pulmonary hypertension as cardiac complications. The prevalence was one-quarter of that found in the aforementioned large meta-analyses, but cardiac iron overload was almost twice as high. The differences between these figures could be explained by differences in the sizes of the studied populations; in addition, we must bear in mind that patients with cardiac iron overload are prone to develop cardiac complications [2]. There were several patients with cardiac iron overload in the region from which the patients studied by the authors of the present study came, similar to reports by Carpenter et al. [19], Aessopos et al. [20], and Ngim et al. [21], which highlight the importance of the region in this regard.

The multifactorial nature of TDT patients' cardiac complications is of interest to physicians regarding 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 a 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]. No significant correlation between ICT and cardiac T2 MRI (p = 0.001) was 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, and their results aligned with our current study.

On another iron overload-related issue, we found a significant correlation between the number of transfusions/ /year and PHT. In line with previous surveys, this result is understandable given that those with more frequent blood transfusions would suffer more from iron overload-related complications [25], although an insignificant number of 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 where necessary. In a previous study regarding endocrine disorders, we looked at the risk effect of splenectomy in developing or compromising low bone mass and endocrinopathies.

Now, given our current results, and based on previous and recent studies, we posit 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 that included roughly half of our population. We reached such a conclusion as well, but serum ferritin was significantly associated with LVEF and cardiac T2 MRI.

Previously at the Shiraz University of Medical Sciences, our colleagues determined that serum ferritin could be an alternative index for determining iron status if T2 MRI was not available [28]. Based on our results, we suggest that relying on serum ferritin could provide a preliminary assessment, but might lead to missing several 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: improvement turned out to be significantly

related. Subsequently, we analyzed serum vitamin D levels with LVEF and cardiac T2 MRI, proving a 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 highlights our patients' compliance and adherence, and reinforces the need for closer monitoring 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, regardless of whether or not there is an underlying disease. However it also happens to be a prominent risk factor in the cardiac status of TDT patients [30]. The negative correlation between LVEF and endocrinopathies calls for closer and more intensive endocrinopathy management among TDT patients with cardiac complications. Since the prevalence of endocrine disorders is more than 80% according to many surveys [3], it could prove challenging to provide acceptable management. We determined that LBM was the most prevalent endocrine disorder in TDT patients in our center, and found it adversely affected LVEF.

The risk of osteoporosis in cardiovascular disease is well established [31], yet the association of low bone mass and cardiac complications in TDT patients has been understudied. The basic etiology of both disorders remains iron overload, but there are differences as to when they developed. LBM can deteriorate the cardiac status of TDT patients. Kyriakou et al. showed that severe cardiac iron status is correlated with low bone mass [32]. We have determined a correlation with heart failure and we suggest the need for intensive bisphosphonate therapy for patients with both low bone 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. As age increases, LVEF decreases significantly and males appeared to have more cardiac complications than females in our study, something which has previously been reported [33]. Therefore, closer cardiac observation is advisable in 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 large population. Our consideration of important associated factors counts as a prominent strength. Despite this, we acknowledge limitations such as a lack of data availability on arrhythmias and the fact that the study was retrospective.

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

Conclusion

We believe that 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 data analysis was significantly related to the incidence of HF and possible PTH. This requires more thorough follow-up on the ICT regimen and patient compliance.

The clinical experience of our hematologist and cardiologist also implies that managing other associated factors such as endocrine disorders, splenectomy rate, and serum vitamin D level lowers the rate of cardiac disorders, and therefore the mortality rate.

Article information and declarations

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Author contributions

HB — main author, design of the study. SK — edited and prepared the manuscript, and was cardiologist involved with our participants. SH — main analyst, provided results, helped with editing. ORZ — helped design of the study, gathered data, edited manuscript.

Conflict of interests

The authors declare no conflict of interests.

Data availability statement

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

Patient consent statement

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

Ethic statement

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

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None.

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