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A Survey on Structural and Functional Cardiac Abnormalities in Transfusion-Dependent Thalassemia, a Report from South-East of Iran

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ABSTRACT

Background: Cardiac abnormalities are common complications in Transfusion Dependent Thalassemia (TDT).

Objectives: This study aimed to assess functional and structural cardiac abnormalities in TDT patients in Zabol, Sistan and Baluchistan province in south-east of Iran.

Patients and Methods: This cross-sectional study was conducted on 85 TDT patients selected via simple random sampling. Demographic information was obtained using a questionnaire. Additionally, clinical and laboratory data were extracted from medical records. Cardiac assessment was conducted by standard Doppler echocardiography. After all, the data was statistically analyzed using the SPSS statistical software, version 19.

Results: In this study, 54 participants (63.5%) were female and 31 ones (36.5%) were male. The participants' mean age was 19.2 ± 6.1 years. In addition, 58 patients (68.2%) had at least one cardiac abnormality. The mean of Left Ventricular Ejection Fraction (LVEF) was 60.3 ± 8.5% (range: 40 - 80%). The most common cardiac conditions were Tricuspid Regurgitation (TR) (58.8%), Left Ventricular Diastolic Dysfunction (LVDD) (43.5%), Pulmonary valve Insufficiency (PI) (35.3%), and Mitral Regurgitation (MR) (32.9%). Moreover, Left Ventricular Systolic Dysfunction (LVSD), Aortic Insufficiency (AI), and pericard effusion were detected in 6 (7.1%), 2 (2.4%), and 2 patients (2.4%), respectively. The results revealed a significant association between LVDD and splenomegaly, splenectomy, hepatomegaly, chelation therapy, and anti-HCV positivity. Indeed, anti-HCV positivity was significantly associated with MR and lower LVEF. Patients with positive anti-HCV results presented a higher risk of cardiac dysfunction (OR = 4.1, 95% CI: 0.8 - 19.8, P = 0.022) and LVEF < 55% (OR = 4.2, 95% CI: 1.2 - 14.9, P = 0.027).

Conclusions: The results indicated anti-HCV positivity as a significant risk factor for heart dysfunction in TDT patients. Thus, cardiac functionality is recommended to be assessed regularly in TDT patients.

1. Background

Thalassemia is the most common monogenic inherited disorder worldwide. This condition results from mutations in either α or β globin genes. It has been estimated that 60 000 thalassemia patients are born across the world annually, the majority of whom reside in south Asia, Middle East, and Mediterranean regions (1, 2). From clinical point of view, thalassemia phenotype may fall into three major phenotypes, including Transfusion Dependent Thalassemia (TDT) requiring regular blood transfusions (> 8 units per year), Thalassemia Intermediate (TI) needing irregular blood transfusions (< 8 units per year), and thalassemia trait that is the asymptomatic variant of the syndrome (2, 3).

Regular blood transfusion is the only way for ensuring a better life expectancy in TDT patients. These patients generally receive more than 20 times higher iron content

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than normal. Excess iron resulting from transfusions exerts multiple detrimental effects on various body organs (4, 5). With saturation of transferrin, the iron binding molecule within plasma, iron will be available in Non-Transferrin Bound Iron (NTBI) that is highly reactive and deleterious for cells. In particular, NTBI can enter cardiac myocytes intervening with myocardium function. This phenomenon is supposed to be the main cause of cardiac abnormal function in TDT (6).

In years before initiating blood transfusions and chelation regimens, heart failure was the major cause of death in TDT. Even today and despite landmark achievements in management of the condition, cardiac events are still the leading cause of death in TDT (3, 7). In Iranian TDT patients, cardiac events are responsible for 19 - 23% of hospitalizations (8, 9). Courtesy of effective iron chelation therapies in the recent years, the frequency and age of onset of heart failure have respectively decreased and increased substantially in TDT. However, heart dysfunction is still the most dreadful complication of TDT in developing countries.

Cardiac derangements in TDT encompass both functional and structural abnormalities. Left Ventricular Systolic Dysfunction (LVSD), Left Ventricular Diastolic Dysfunction (LVDD), and pericarditis are among the most frequently encountered heart abnormalities in TDT patients (10). Systolic and diastolic heart dysfunctions may be observed in even very young ages worsening through the time. Therefore, significant efforts have been dedicated to finding reliable risk factors predicting the risk of heart failure in TDT patients. However, these studies have been inconclusive (3, 11, 12).

Regular evaluation of cardiac function is recommended for early identification of heart abnormalities even in TDT. Doppler echocardiography-derived functional indices, such as systolic and diastolic functions, and structural indices, such as Mitral Regurgitation (MR) and Tricuspid Regurgitation (TR), have been shown to have predictive values for cardiac iron overload in TDT (13). Doppler echocardiography continues as a reliable procedure for assessing heart function in TDT patients, especially in low-income nations (14).

2. Objectives

Sistan and Baluchistan province in southeast of Iran is one of the regions with a large number of TDT patients in the country. Zabol is the biggest city in north of the province with high thalassemia penetrance. As there were no previous reports on cardiac dysfunction in TDT patients in the city, the present study aims to assess cardiac abnormalities in 85 TDT patients registered at Thalassemia Care Center of Imam Khomeini Hospital of Zabol.

3. Patients and Methods

3.1. Patients

The current cross-sectional study was carried out on 85 TDT patients registered at Thalassemia Care Center at Imam Khomeini Hospital of Zabol, Sitan and Baluchistan province during July-November 2016. The patients were recruited via simple random sampling. These patients had been receiving care since their diagnosis at the center and received blood transfusions every 2 - 4 weeks. The study was approved by the Ethics Committee of Zabol University of Medical Sciences. Indeed, informed consent forms were obtained from the patients or their parents before enrollment into the study.

Demographic data were acquired through interviews and a short questionnaire. Additionally, clinical and laboratory variables were obtained based on the results of the latest archived check-ups available in the patients' medical records.

3.2. Inclusion and Exclusion Criteria

The patients receiving at least 10 red blood cell units were included in the study. However, the patients with diabetes mellitus and other endocrinopathies (hypothyroidism or hypoparathyroidism) and malignancies, those with evidences of clinical cardiac disease, and those who were under treatment for cardiovascular diseases were excluded from the study.

3.3. Doppler Echocardiography

Standard M-mode, two-dimensional Doppler echocardiography was performed for each patient at rest condition one week after the latest blood transfusion (5). LVSD, LVDD, contraction patterns of the heart, and structure and function of mitral, pulmonary, aorta, and tricuspid valves were evaluated. The results were interpreted by an experienced cardiologist.

3.4. Statistical Analysis

Statistical analysis was carried out using the SPSS statistical software, version 19. Normality of the data was scrutinized by Shapiro-Wilk test. Descriptive statistics were used to demonstrate frequencies and mean values for qualitative and quantitative variables, respectively. In univariate analysis, chi-square test was applied to seek for the potential association between qualitative variables and cardiac conditions. On the other hand, independent sample t-test and one-way ANOVA were exploited for comparison of the groups with respect to the mean values of quantitative variables. Finally, logistic regression was performed at Entry Method to explore the potential association between cardiac dysfunction and sex, age, organomegalies, anti-HCV positivity, ferritin level, and chelation regimens.

4. Results

Out of the 85 patients, 54 (63.5%) were female and 31 (36.5%) were male. The patients' mean age was 19.2 ± 6.1 years (range: 5 - 40 years). Besides, 20 patients (25.6%) were below 15 years old, 45 patients (57.7%) were 15 - 25 years old, and 13 patients (16.7%) aged > 25 years. Chelation regimens included monotherapy with Deferoxamine (DFO) (15, 176.6%), Iranian synthetic Deferasirox (Osveral) (28, 32.9%), combination therapy with DFO + Deferiprone (DFP) (34, 40%), and DFO + Osveral 8 (9.4%). Hepatomegaly was present in 21 patients (25%). Additionally, positive anti-HCV was observed in 16 patients (19.3%), while 2 patients (2.4%) had positive HBs Ag. Moreover, the mean ferritin value was 5438.6 ± 3412.8 ng/mL, and the mean value of maximum ferritin in the past two years was 8089.5 ± 3542.6 ng/mL.

At least one cardiac dysfunction was observed in 58 patients (68.2%). However, 27 patients (31.8%) represented with normal heart function. LVDD comprised the most common heart functional abnormality (34/85, 40%). Considering valve abnormalities, concomitant MR + TR + Pulmonary valve Insufficiency (PI) was the most common condition (16/85, 19%, Table 1).

The results showed no significant association between sex and either systolic or diastolic dysfunctions and structural valve abnormalities. However, there was a significant association between LVDD and chelation regimens. Accordingly, 20 patients (54%) with LVDD were using

Table 1. The Frequency of Cardiac Abnormalities in Echocardiographic Examination of 85 TM Patients

Cardiac Abnormalities		Total (n = 85), n (%)
Heart functional abnormalities	Normal	45 (52.9)
	LVSD	4 (4.7)
	LVDD	34 (40)
	LVSD + LVDD	2 (2.4)
Heart valve abnormalities	Normal	29 (34.5)
	MR	4 (4.8)
	PI	1 (1.2)
	TR	15 (17.9)
	AI	1 (1.2)
	MR + TR	6 (7.1)
	TR + PI	13 (15.5)
	MR + TR + PI	16 (19)

Abbreviations: LVSD, left ventricular systolic dysfunction; LVDD, left ventricular diastolic dysfunction; MR, mitral regurgitation; PI, pulmonary valve insufficiency; TR, tricuspid regurgitation

Table 2. The Relationship between Demographic and Clinical Variables and Common Cardiac Abnormalities Observed in 85 TM Patients

Variables		Cardiac Abnormalities				
		LVSD [a], n = 6 [b], n (%)	**LVDD, n = 36 [b], n (%)**	**MR, n = 26 [b], n (%)**	**PI, n = 30 [b], n (%)**	**TR, n = 50 [b], n (%)**
Sex	Male	3 (50)	10 (27.7)	11 (42.3)	11 (36.6)	21 (42)
	Female	3 (50)	26 (72.3)	15 (57.7)	19 (63.4)	29 (58)
	P	0.311	0.128	0.420	0.594	0.112
Age (years)	< 15	1 (16.6)	2 (5.6)	5 (19.2)	10 (33.5)	13 (26)
	15 - 25	3 (50)	23 (63.8)	16 (61.6)	16 (53.3)	29 (58)
	> 25	2 (33.4)	11 (30.6)	5 (19.2)	4 (11.2)	8 (16)
	P	0.975	0.001 c	0.619	0.530	0.695
Chelation drug	DFO	3 (50)	10 (27.7)	6 (23.1)	3 (10)	7 (14)
	DFO + DFP	1 (16.6)	19 (52.8)	8 (30.6)	9 (30)	18 (36)
	Osveral	2 (33.4)	7 (19.5)	9 (34.8)	15 (50)	20 (40)
	DFO + Osveral	0 (0)	0 (0)	3 (11.5)	3 (10)	5 (10)
	P	0.133	0.009	0.428	0.072	0.362
Spleen status	Normal	0 (0)	2 (5.6)	3 (11.5)	6 (20)	7 (14)
	Splenomegaly	2 (33.4)	10 (27.7)	2 (7.6)	8 (26.7)	14 (28)
	Splenectomy	4 (66.6)	24 (66.7)	21 (80.9)	16 (53.3)	29 (58)
	P	0.485	0.026	0.007	0.802	0.312
Liver status	Normal	4 (66.6)	22 (61.2)	20 (80.9)	25 (83.3)	38 (76)
	Hepatomegaly	2 (33.4)	14 (38.8)	6 (23.1)	5 (16.7)	12 (24)
	P	0.483	0.033	0.413	0.181	0.559
Ferritin (ng/mL)	< 5000	3 (50)	15 (41.7)	15 (57.6)	19 (63.3)	30 (60)
	5000-8000	2 (33.4)	14 (38.8)	9 (34.8)	6 (20)	10 (20)
	> 8000	1 (16.6)	7 (19.5)	2 (7.6)	5 (16.7)	10 (20)
	P	0.815	0.105	0.183	0.596	0.343
Anti-HCV	Negative	3 (50)	23 (63.8)	20 (76.9)	24 (80)	37 (74)
	Positive	3 (50)	13 (36.2)	6 (23.1)	5 (20)	13 (26)
	P	0.148	0.0001	0.377	0.404	0.110
Cardiac abnormalities	LVSD	-	2 (5.5)	5 (19.2)	4 (13.3)	6 (12)
	P	-	0.0001	0.011	0.115	0.038
	LVEF < 55%	6 (100)	5 (13.8)	11 (42.3)	10 (33.3)	17 (34)
	P	0.0001	0.0001	0.003	0.028	0.0001

Abbreviations: LVSD, left ventricular systolic dysfunction; LVDD, left ventricular diastolic dysfunction; MR, mitral regurgitation; PI, pulmonary insufficiency; TR, tricuspid regurgitation; LVEF, left ventricular ejection fraction; DFO, deferoxamine; DFP, deferiprone Fisher's exact test; [a], Statistically significant values in bold. [b], Including patients with combined abnormalities.

the combination of DFO + DFP, while none of the patients with combination of DFO + Osveral showed LVDD (P = 0.009). In univariate analysis, the patients with splenectomy showed a significantly higher ratio of LVDD (25/37, 67.5%) compared to those with splenomegaly (10/37, 27%) and normal spleen (2/37, 5.5, P = 0.01). The patients with splenectomy also showed a significantly higher frequency of MR (21/28, 75%, P = 0.007). Moreover, the results revealed a significant association between hepatomegaly and diastolic dysfunction (P = 0.031). Furthermore, 14/16 patients (87.5%) with anti-HCV positive results had cardiac dysfunction (P = 0.045). There was a significant association between anti-HCV positivity and LVDD (P < 0.001). The results of the associations between cardiac dysfunction and different demographic and clinical features have been presented in Table 2.

The mean Left Ventricular Ejection Fraction (LVEF) was recorded as 60.3 ± 8.5% (range: 40 - 80%). The results indicated no significant relationships between LVEF and demographic and clinical features, such as sex, drug chelation, and spleen or liver status. However, the patients with positive anti-HCV had lower LVEF (56 ± 7.9%) compared to those with negative anti-HCV (61.8 ± 7.8%, P = 0.012, Table 3). In logistic regression analysis, anti-HCV positivity was significantly associated with a higher risk of cardiac dysfunction (OR = 4.1, 95% CI: 0.8 - 19.8, P = 0.022) and LVEF < 55% (OR = 4.2, 95% CI: 1.2 - 14.9, P = 0.027, Table 4).

5. Discussion

Cardiac failure is the major cause of mortality in TDT patients. In the present study, the frequency of common heart abnormalities was assessed in 85 Iranian TDT patients. Cardiac dysfunction was detected in 58/85 TDT patients (68.2%) in this study. Besides, the mean LVEF was 60.3 ± 8.5%. In a study on 66 Iranian TDT patients, LVEF was 60 ± 7% (15). Amoozgar et al. also reported the mean LVEF values of 69.9 ± 8.2% and 72.9 ± 8.8% in Iranian patients with TDT and TI, respectively (16). In another Iranian study on 80 TDT and 22 TI patients, LVEF values were 59.1 ± 6.5% and 61.5 ± 7.1%, respectively (12). In a study on TDT patients in Turkey, the mean LVEF was reported as 61 ± 7.6% (17). In Egyptian TDT patients, the mean LVEF was 67.7 ± 4.7% (18). It has been argued that even an LVEF of as high as 62% might be considered below the normal range for these patients (19). Accordingly, a threshold of 60% has been proposed as the normal value in these patients (20). In accordance, LVEF in TDT patients has been comparable with that of matched controls. Generally, left ventricular function is usually preserved in TDT patients, which seems to be a result of higher cardiac output in these patients (20).

The current study results revealed no significant correlation between LVEF and ferritin level. Nonetheless, some studies have found a correlation between LVEF and ferritin level in TDT patients (15, 21). On the other hand, the findings of some other reports are in line with those of

Table 3. The Mean Values of Selected Variables in 85 Transfusion-Dependent Thalassemia Patients with and Without Cardiac Abnormalities

Variables		Age (Years) Mean ± SD	Maximum Ferritin (ng/dL) Mean ± SD	WBC (103/µL) Mean ± SD	Platelet ([a] 103/µL) Mean ± SD	AST (IU/L) Mean ± SD	LVEF %
Anti-HCV	Positive (n = 15)	22.9 ± 6.2	8174.3 ± 2032.9	12.5 ± 6.3	338.6 ± 186.8	73.4 ± 44.6	56 ± 7.9
	Negative	18 ± 5.5	8122.6 ± 3828.3	12.4 ± 9.1	366.7 ± 212.2	53.4 ± 42.7	61.8 ± 7.8
	P	0.004 [a]	0.947	0.934	0.656	0.129	0.017
LVSD	Normal (n = 76)	18.8 ± 6	8122.8 ± 3669.7	12.2 ± 7.6	366.8 ± 212.1	56.9 ± 44.5	61.5 ± 7.5
	Abnormal (n = 6)	22.8 ± 6.7	7625 ± 1880.3	19.3 ± 16.8	290.1 ± 54.2	56.1 ± 26.8	44.8 ± 2.8
	P	0.109	0.904	0.032	0.025	0.953	< 0.0001
LVDD	Normal (n = 48)	16.6 ± 5.4	7484.5 ± 3790	11.6 ± 9.2	326.3 ± 152.9	51 ± 43.5	59.1 ± 8.9
	Abnormal (n = 37)	22.3 ± 5.3	9026.1 ± 3057.2	13.7 ± 7.8	413 ± 257.3	64.2 ± 42.8	63.4 ± 5.9
	P	< 0.0001	0.043	0.230	0.067	0.161	0.019
Mitral valve	Normal (n = 56)	18.1 ± 5.8	8363.3 ± 3790.4	10.9 ± 7.4	320.8 ± 190.2	63 ± 49.4	62.6 ± 7.5
	MR	21.4 ± 6.2	7521.5 ± 2948.4	16.2 ± 9.9	4396.3 ± 214.6	42.2 ± 19.6	55.7 ± 8.6
	P	0.023	0.309	0.008	0.016	0.030	< 0.0001
Pulmonary valve	Normal (n = 55)	19.6 ± 5.8	8258.9 ± 3443.8	11.8 ± 7.7	357.2 ± 212.9	63.4 ± 48.1	63.7 ± 7.5
	PI	18.3 ± 6.5	7774 ± 3761.2	14.2 ± 10.2	363.9 ± 192	43.7 ± 27.5	54.2 ± 6.5
	P	0.306	0.534	0.282	0.812	0.058	< 0.0001
Tricuspid valve	Normal (n = 35)	19 ± 6.3	8467.6 ± 3723.4	11 ± 7.3	352.7 ± 233.9	60.1 ± 49.2	66.3 ± 4.6
	TR	19.3 ± 5.9	7813.8 ± 3418	13.8 ± 9.4	364.4 ± 183.4	54.2 ± 38.5	56 ± 8
	P	0.889	0.422	0.114	0.701	0.597	< 0.0001

Abbreviations: WBC, white blood cells count; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; LVDD, left ventricular diastolic dysfunction; MR, mitral regurgitation; PI, pulmonary insufficiency; TR, tricuspid regurgitation. [a], Statistically significant values in bold.

Table 4. Logistic Regression Analysis for Selected Variables Predicting the Risk of Cardiac Abnormalities and LVEF < 55% in TM Patients

Variables		Cardiac Abnormalities			LVEF < 55%		
		Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Sex	Female	Reference			Reference		
	Male	1	0.4 - 2.6	0.997	0.3	0.1 - 0.9	0.041 [a]
Age groups (years)	< 15	Reference			Reference		
	15 - 25	3	1 - 9.3	0.044	0.8	0.2 - 3.3	0.802
	> 25	1.6	0.3-6.6	0.566	0.7	0.1 - 4.6	0.786
Chelation drug	DFO	Reference			Reference		
	Osveral	0.9	0.2 - 3.7	0.834	0.9	0.2 - 3.8	0.923
	DFO + DFP	0.7	0.1 - 2.9	0.650	0.3	0.08 - 1.7	0.246
	DFO + Osveral	0.3	0.06 - 2.1	0.267	0.9	0.1 - 6.5	0.965
Spleen status	Normal	Reference			Reference		
	Splenomegaly	0.9	0.2 - 3.3	0.831	1	0.3 - 2.8	0.474
	Splenectomy	2.2	0.6 - 7.9	0.204	1.9	0.5 - 6.7	0.624
Liver status	Normal	Reference			Reference		
	Hepatomegaly	1.2	0.4 - 3.6	0.663	0.9	0.2 - 3.3	0.947
Ferritin level (ng/mL)	< 5000	Reference			Reference		
	5000 - 8000	1	0.2 - 3.5	0.960	1.4	0.4 - 5.4	0.555
	> 8000	1.5	0.3 - 6.6	0.521	0.2	0.03 - 2.6	0.203
Anti-HCV antibody	Negative	Reference			Reference		
	Positive	4.1	0.8 - 19.8	0.024	4.2	1.2 - 14.9	0.025

Abbreviations: LVEF, left ventricular ejection fraction; DFO, deferoxamine; DFP, deferiprone. [a], Statistically significant values in bold

the present study (16, 18, 22). The reliability of ferritin as a predictor of body iron content in TDT is under question (5, 13). Iron overload within cardiomyocytes is assumed to be the major pathological cause of cardiac dysfunction in TDT. Excessive iron within cells can interfere with different cellular functions, such as enzymatic activities and energy production (3). Oxidation of biomolecules, such as membrane phospholipids, proteins, and nucleic acids, by free reactive iron species can lead to apoptosis and organ fibrosis (10). Furthermore, impaired mitochondrial respiratory chain in cardiomyocytes may exert detrimental effects on contractibility of these cells, provoking heart failure (23). In parallel, chelation regimens with ability to remove iron from cardiomyocytes can be effective in improving LVEF in TDT patients (19). Nevertheless, no significant differences were found between LVEFs in TDT patients with different chelation regimens in the present study. This might be due to poor compliance of our patients with chelation therapies.

The results of the current study revealed a significant relationship between LVEF and positive anti-HCV state. Consistently, hepatitis C seropositive state was significantly associated with cardiac dysfunction in Egyptian TDT patients (24). A recent study also indicated that chronic HCV infection was related to cardiac fibrosis (25). HCV has been shown as a potential contributing factor in cardiovascular abnormalities in some clinical conditions (26, 27). However, further studies have to be conducted on the role of HCV in cardiac dysfunction in TDT.

In the present study, LVSD was observed in 6 patients (7.1%). The results of univariate analysis showed no significant relationships between LVSD and age, type of chelation therapy, spleen condition, liver status, ferritin level, and HCV seropositive status. These results are similar to the findings obtained by Morsy et al. (28) and Noori et al. (12). In a 10-year follow-up of 315 TDT patients by Aessopos et al., 12 were identified with LVSD. However, no significant differences were found between the systolic dysfunction group and normal systolic function group regarding ferritin level, age, and pre-transfusion hemoglobin (29).

The current study findings demonstrated a significant association between LVSD and LVDD ($P < 0.001$). Similarly, Aessopos et al. reported that patients with LVSD had a higher rate of LVDD (29). Our study results also showed that the patients with LVSD had a higher rate of MR ($P = 0.01$) and TR ($P = 0.03$). LVSD is a relatively low-prevalence condition in TM. Yet, special attention should be paid to patients who develop this condition.

LVDD was a common cardiac dysfunction in the present study (37/85, 43.5%). Indeed, the results indicated that LVDD was significantly associated with higher ages, type of drug chelator (lower prevalence in the group with combination of DFO and Osveral), splenomegaly and splenectomy, hepatomegaly, and anti-HCV positivity. In addition, the maximum ferritin level in the last two years was significantly higher in the patients with LVDD. In the study by Silvilairat et al., 100% of the patients with ferritin > 5000 ng/mL presented with LVDD (14). In contrast, none of the TDT patients with ferritin < 2500 ng/mL had LVDD in that study (14). LVDD was also significantly higher in splenectomized TDT patients compared to those with normal spleens (13, 28). Although some etiological factors, such as thrombocytosis, hypercoagulability, splenectomy, and pulmonary hypertension, have been noted for LVDD, the role of direct iron toxicity might be more pronounced in this process. Generally, it is believed that cardiac diastolic abnormalities are developed before systolic dysfunction (23). Considering the fact that LVDD is among the primary signs of cardiac dysfunction, it is recommended to closely monitor the patients with this abnormality and advise the

patients to undertake appropriate iron chelation therapy to reverse the conditions or prevent its progression.

Regarding valve abnormalities, TR (58.8%) was the most common observed condition followed by PI (35.3%) and MR (32.9%). In the study by Wu KH et al., 30.8% of TDT patients had TR (30). In the current study, the patients with TR had significantly lower LVEF, which is in accordance with the results of the researches performed by Wu et al. (30) and Mohammad et al. (31). Furthermore, development of MR was significantly associated with higher ages, higher leukocyte and platelet counts, and lower LVEF in our study. Likewise, Rafsanjani et al. obserevd that TDT patients with MR had higher platelet counts (32). Overall, special attention to valve abnormalities is crucial in TDT patients to prevent advanced acute conditions.

Cardiac abnormalities are among the common transfusion-related complications in TDT patients. Because of the high rate of morality associated with heart failure, identification of the patients at early stage of cardiac dysfunction is essential. Diastolic dysfunction and valve structural abnormalities are relatively common cardiac abnormalities in TDT. Thus, it is recommended to proceed with an appropriate chelation therapy in TDT patients with cardiac conditions to prevent and even reverse these abnormalities.

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Authors' Contribution

Ali Bazi, literature review, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript edition, and manuscript review; Iraj Shahramian, concept, design, definition of intellectual content, clinical studies, data acquisition, manuscript preparation, manuscript edition, and manuscript review; Zohre Mahmoodi, concept, design, definition of intellectual content, clinical studies, echocardiography performance, data acquisition, manuscript edition, and manuscript review; Nosratollah Masinaeinezhad, Ali Khosravi Bonjar, and Amin Safa, data acquisition, data analysis, statistical analysis, and manuscript review; Mojtaba Delaramnasab, literature review, data acquisition, statistical analysis, and manuscript review.

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