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Original Article

Risk Factors Associated With Heart Failure in Patients With β-Thalassemia

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ABSTRACT

Background: Inherited hemoglobin disorders such as thalassemia are among the most critical public health concerns. Heart failure (HF) is one of the essential complications in β-thalassemia patients. Cardiac iron accumulation is the single greatest risk factor for cardiac dysfunction in thalassemia. Our study aimed to determine factors associated with HF in β-thalassemia patients.

Methods: This was a retrospective cohort study on 2913 patients with thalassemia. Thorough medical history taking and physical examinations were done for a basic cardiac assessment, including 12-lead electrocardiography and detailed echocardiography, according to the guidelines. Cardiac magnetic resonance imaging was used to evaluate cardiac iron overload (T2), which was an invaluable tool to estimate the clinical risk and the development of heart complications in the patients. A logistic regression model was used in SPSS, version 23.0, to assess HF factors. The Hosmer–Lemeshow test and ROC curve were used for goodness of fit.

Results: Overall, 14.69% of the patients had HF. The logistic regression model showed that thalassemia major, older age, higher hemoglobin, higher ferritin, later initiation, iron chelators, more blood transfusion, and comorbidities increased the risk of HF in thalassemia patients. The adjusted area under the ROC curve in the logistic regression model was 0.79.

Conclusions: Most factors related to an increased risk of HF in thalassemia patients were controllable. The timely onset of transfusions and iron chelator therapy, as well as long-life follow-up, can help detect cardiac involvement and treat the disease early. ***(Iranian Heart Journal 2022; 23(3): 88-96)***

KEYWORDS: Heart failure, β-thalassemia, Factors

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Beta-thalassemia is an inherited hemoglobin disorder leading to chronic hemolytic anemia, which requires life-long transfusion therapy.[1] The World Health Organization (WHO) identified thalassemia as the world's most common chronic genetic disorder, affecting about 100 000 children each year.[2]

Geographically, parts of Africa, Turkey, Iran, the Netherlands, and Southeast Asia are called "the global thalassemia belt".[3] The iron deposition, related to transfusions, causes a cytotoxic effect in many organs such as the heart, liver, and endocrine glands. The most important leading causes of death in β-thalassemia patients with chronic blood transfusion are cardiac complications, which have been attributed to secondary iron overload despite timely chelation. An estimated 18 000 deaths from thalassemia occurred in 2010.[4-8]

Major cardiac disorders in major thalassemia patients include left ventricular systolic dysfunction, diastolic dysfunction, pulmonary hypertension, valvular diseases, arrhythmias, and pericarditis.[10] Cardiac function represents the primary determinant of survival in transfusion-dependent thalassemia patients. Mainly with increased survival rates, other manifestations of thalassemia have become apparent. Treated patients are likely to live longer; nonetheless, when heart failure (HF) symptoms appear, lifespan rapidly decreases. The major complication affecting the heart is HF due to the accumulation of iron in myocytes. The cardiovascular complications of thalassemia can be considered in 2 major clinical categories: 1) iron overload complications, including reversible up to irreversible myocyte failure, arrhythmias, and arterial involvement (eg, loss of vascular compliance) and 2) non-iron overload complications, including pulmonary hypertension.

Regularly repeated blood transfusions are used for the average growth and maintenance of healthy life in these patients. Frequent blood transfusions can increase iron stores in the body. Iron deposition in various sensitive organs such as the liver, glands, and heart ultimately leads to significant complications including liver cirrhosis, cardiac disorders, osteoporosis, hepatitis, diabetes, and hypothyroidism.[12] The availability of 3 chelating agents has a practical impact on the debate on the regimen of chelation therapy. Optimum treatment is now prescribed by the toxicity or adverse effects such as agranulocytosis and liver or renal dysfunction. Renal dysfunction is a known independent risk factor for a rise in cardiac disease and death.

The clinical presentation of HF is variable. Right HF symptoms, including neck vein distension, hepatomegaly, and peripheral edema, are often the first clinical signs. Rapid decompensation with predominant right HF features (eg, an acute abdomen) and painful hepatomegaly can be mistaken for cholangitis or biliary obstruction.

Classic left HF features, including rales, crackles, dyspnea on exertion, and orthopnea, comprise late findings. A combination of conventional and tissue Doppler echocardiography should be used to evaluate diastolic function. Isolated diastolic dysfunction can occur; nevertheless, it is relatively rare, and patients are asymptomatic.

The present study was conducted to determine the critical predictor of cardiac complications in β-thalassemia.

METHODS

The current retrospective cohort study recruited 2913 patients with thalassemia admitted to the thalassemia wards of the Iranian cities of Tehran, Shiraz, Zahedan, Sari, Rasht, Bandar Abbas, and Bushehr to receive transfusions. The patients recruited had active medical records. The hospitals in the center of the aforementioned cities, which were considered thalassemia reference hospitals, were regarded as clusters. From among the

centers, one center was selected at random, and all the patients referred to that center were enrolled in the study. Thorough medical history taking and physical examinations were done for a basic cardiac assessment, which included 12-lead electrocardiography and detailed echocardiography, according to the guidelines. A combination of conventional and tissue Doppler echocardiography was used to evaluate cardiac function. Serial transthoracic echocardiography was repeated once a year for all the patients, and special echocardiography by an expert cardiologist was done to evaluate patients with HF. Cardiac magnetic resonance imaging (CMR) was used to evaluate cardiac iron overload (T2), which was an invaluable tool in the estimation of clinical risk and the development of heart complications in the patients. Serial CMR was repeated every 3 years for patients with iron-mediated cardiac failure.

Data were collected using a researcher-made checklist and checking the patients' active files. The checklist included demographic characteristics (eg, sex, age, weight, type of thalassemia, marital status, type of parental marriage, patients' and parents' education levels, and patients' and parents' occupations), clinical information (eg, laboratory findings concerning ferritin, hemoglobin, age at the onset of iron therapy, and the amount of blood consumed), medical history (eg, treatment pain), and medical history of diabetes, liver disease, and coinfections (HCV-HBV). Patients with HF diagnosed by a physician were included.

Statistical Analysis

Descriptive statistics of quantitative variables were reported using the mean ± the standard deviation (SD). Qualitative variables were reported using frequencies and percentages.

The statistical analyses were conducted using the independent samples *t* test for continuous variables and the χ^2 test for categorical variables. For the identification of the factors related to HF, univariate and multivariate logistic regression analyses were utilized. The backward method was employed, and variables with a *P* value of less than 0.25 in the simple logistic regression were included in the model to fit the multivariate logistic regression. The Hosmer–Lemeshow test and a receiver operating characteristic curve (ROC) were used to fit the model.

All the data were analyzed at a significance level of less than 0.05, with a 95% confidence interval (CI) using the SPSS software, version 23.0.

RESULTS

Overall, 428 of the 2913 thalassemia patients had HF. The mean age of the patients with HF was 26.18±10.61 years. The study population included 210 male patients. Further, 347 patients had β-thalassemia major and 68 patients had β-thalassemia intermedia. Regarding age at the onset of chelator therapy in the patients with HF, 261 patients were over 6 years of age. Additionally, 97 patients had a hemoglobin level of less than 9 g/dL, and 149 had a serum ferritin level of less than 2500 ng/mL. The mean blood consumption amount was 586.93±148.71. Diabetes was reported in 104 patients, liver disease in 35, and coinfections in 53 (HBV-HCV).

Among the assessed factors, composed of thalassemia type, age at the initiation of chelators, hemoglobin levels, ferritin levels, blood consumption, diabetes, liver disease, and coinfections, there were statistically significant differences between the patients who had HF and those who did not.

The details of the demographic and clinical characteristics of the study population are summarized in Table 1.

The multivariate logistic regression analysis suggested that HF was closely related to age, type of thalassemia, age at the initiation of chelators, hemoglobin levels, ferritin levels, the amount of blood consumed, and coinfections.

Table 1: Distribution of the demographic and clinical characteristics of the β-thalassemia patients with and without heart failure in Iran

Variables	Heart Failure (428)	No Heart Failure (2485)	*P* value
Age	26.18 ± 10.61	26.11 ± 11.96	0.91
Sex			0.76
Male	210 (14.5%)	1242 (85.5%)	
Female	208 (14.9%)	1191 (85.1%)	
Thalassemia Type			0.01
Intermedia	68 (11.8%)	499 (88.2%)	
Major	347 (16.1%)	1819 (83.9%)	
Marital Status			0.24
Married	50 (13.2%)	329 (86.8%)	
Single	342 (15.5%)	1866 (84.5%)	
Consanguineous Marriage			0.23
Yes	234 (15.8%)	1251 (84.2%)	
No	171 (14.1%)	1040 (85.9%)	
Age at the Initiation of Chelators (mon)			0.003
< 24	36 (11.1%)	288 (88.9%)	
24 – 72	60 (21.1%)	224 (78.9%)	
> 72	261 (17.9%)	1293 (82.1%)	
Annual blood transfusion rate	586.93 ± 148.71	443.18 ± 193.85	<0.001
Treatment Discomfort			0.26
Easy	73 (13.7%)	460 (86.3%)	
Difficult	148 (15.9%)	784 (84.1%)	
Hemoglobin (g/dL) Before Transfusion			<0.001
≤ 9	97 (10.2%)	852 (89.8%)	
> 9	253 (16.9%)	1242 (83.1%)	
Ferritin (ng/mL)			0.03
≤ 2500	149 (47.7%)	1103 (88.1%)	
≥ 2500	174 (14.9%)	994 (85.1%)	
Diabetes			<0.001
No	323 (12.3%)	2301 (87.7%)	
Yes	104 (36.1%)	184 (63.9%)	
Liver Disease			<0.001
No	393 (14.0%)	2423 (86.0%)	
Yes	35 (36.1%)	62 (63.9%)	
Coinfections			<0.001
No	375 (13.4%)	2423 (86.6%)	
Yes	53 (46.1%)	62 (53.9%)	

Table 2 illustrates the factors associated with HF among the β-thalassemia patients. HF was associated with thalassemia major (OR=1.88; 95% CI, 1.20 to 3.83), aging (OR=1.03; 95% CI, 1.01 to 1.06), higher ferritin levels (OR=5.73; 95% CI, 3.57 to 9.21), older age at the onset of chelation (OR=4.34; 95% CI, 2.37 to 8.26), higher annual transfusion rates (OR=1.005; 95% CI, 1.004 to 1.006), comorbidities (diabetes: OR=2.87; 95% CI, 1.91 to 4.31 and liver disease: OR=2.48, 95% CI: 1.09 to 5.64), and coinfections (OR=5.26, 95% CI, 2.85 to 9.70).

Table 2: Factors related to heart failure among the β-thalassemia patients

	Crude		Adjusted	
Heart Failure	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	1.00 (0.99 – 1.00)	0.91	1.03 (1.01 – 1.06)	0.001
Sex				
Male	1	-	1	-
Female	1.03 (0.83 – 1.27)	0.76	1.18 (0.86 – 1.62)	0.29
Thalassemia Type				
Intermedia	1	-	1	-
Major	1.42 (1.08– 1.88)	0.01	1.88(1.20– 3.03)	0.006
Marital status				
Married	1	-	1	-
Single	1.20 (0.87 – 1.65)	0.25	-	
Consanguineous Marriage				
Yes	1	-	1	-
No	0.87 (0.71 – 1.08)	0.23	-	-
Age at the Initiation of Chelators (mon)				
< 24	1	-	1	-
24 – 72	2.14 (1.36 – 3.35)	0.001	2.43 (1.22- 4.85)	0.01
> 72	1.74 (1.20 – 2.52)	0.003	4.43 (2.37 – 8.26)	<0.001
Annual blood transfusion rate	1.001 (1.001 – 1.002)	<0.001	1.005 (1.004– 1.006)	<0.001
Treatment Discomfort				
Easy	1	-	1	-
Difficult	1.19 (0.87 – 1.61)	0.26	-	-
Hemoglobin (g/dL) Before Transfusion				
≤ 9	1	-	1	-
> 9	1.78 (1.39 – 2.29)	<0.001	1.46 (1.04 – 2.06)	0.02
Ferritin (ng/mL)				
≤ 2500	1	-	1	-
≥ 2500	1.29 (1.02 – 1.63)	0.03	5.73 (3.57 – 9.21)	<0.001
Diabetes				
No	1	-	1	-
Yes	4.02 (3.08 – 5.26)	<0.001	2.87 (1.91 – 4.31)	<0.001
Liver Disease				
No	1	-	1	-
Yes	3.48 (2.26 – 5.33)	<0.001	2.48 (1.09 – 5.64)	0.03
Coinfections				
No	1	-	1	-
Yes	5.52 (3.76 – 8.09)	<0.001	5.26 (2.85 – 9.70)	<0.001

Finally, the Hosmer–Lemeshow test and the ROC curve were used to evaluate the logistic regression results in terms of goodness of fit. The results of the Hosmer- Lemeshow test were not statistically significant, and the area under the curve (AUC) was computed to be 0.79 in the logistic regression.

DISCUSSION

In the present study, older age, older age at the start of the iron chelator, higher serum ferritin levels, higher rates of blood transfusion, and coinfections were associated with a higher HF incidence rate.

Detterich et al[22] (2011) reported that their patients with heart disease were older. Generally, the first manifestation in their young patients was an impaired left ventricular filling pattern with evidence of an abnormal relaxation pattern, while systolic function was normal, and the patients were asymptomatic.

Vahidi et al[23] (2011) also found a positive relationship between age and cardiac disease, consistent with our study results. Kompani et

al[24] (2008) reported that the mean level of ferritin in their patients with thalassemia major was significantly higher than that in their patients with thalassemia intermedia. In our study, higher serum ferritin levels showed a reverse correlation with the left ventricular ejection fraction. Wood et al[25] found that iron overload increased the risk of next cardiac dilatation and decreased cardiac function. Rahimi Bashar et al[26] (2006) found a relationship between ferritin levels and heart disease. Serum ferritin is a widely used indicator of iron overload, and it was independently and significantly associated with the risk of heart disease. High serum ferritin can be a predictor of heart disease risk. Riahifar et al[28] (2018) showed a positive correlation between a lower age at starting iron chelation and a higher survival rate. Borgna–Pignotti et al[29] (2004) found that the risk of cardiac complications was higher in patients receiving chelation therapy in late stages. Farhang et al[30] demonstrated that a pre-transfusion hemoglobin level of less than 9 g/dL could affect cardiovascular function. Bosi et al[25] (1997–2000) also showed that left ventricular size at the end of the diastole was more extensive in patients with a pre-transfusion hemoglobin level of less than 9 g/dL. These results are inconsistent with the results of the present study.

Christoforidis et al[31] (2006) reported a significant relationship between iron overload in the liver and the heart, consistent with our study. In contrast, Leung et al[32] (2009) find no significant relationship between iron overload in the liver and the heart. Shamsian et al[33] (2007) reported that their patients affected by hepatitis C had higher ferritin serum levels than their subjects who were not affected. Kayhanian et al[34] (2011) also revealed that older age, higher serum ferritin levels, higher annual transfusion rates, and older age at starting iron chelation therapy correlated with a higher prevalence rate of diabetes mellitus.

Noursalehi et al[35] (2004) proposed that cardiac dysfunction was more significant in patients with higher annual transfusions, consistent with our study.

Pericarditis and chronic HF due to myocardial hemosiderosis usually occur during the second decade. The mechanisms of iron-mediated myocardial damage are related to direct free iron toxicity in myocytes, increased oxidative damage to lipids and proteins, and immune-mediated mechanisms.[36]

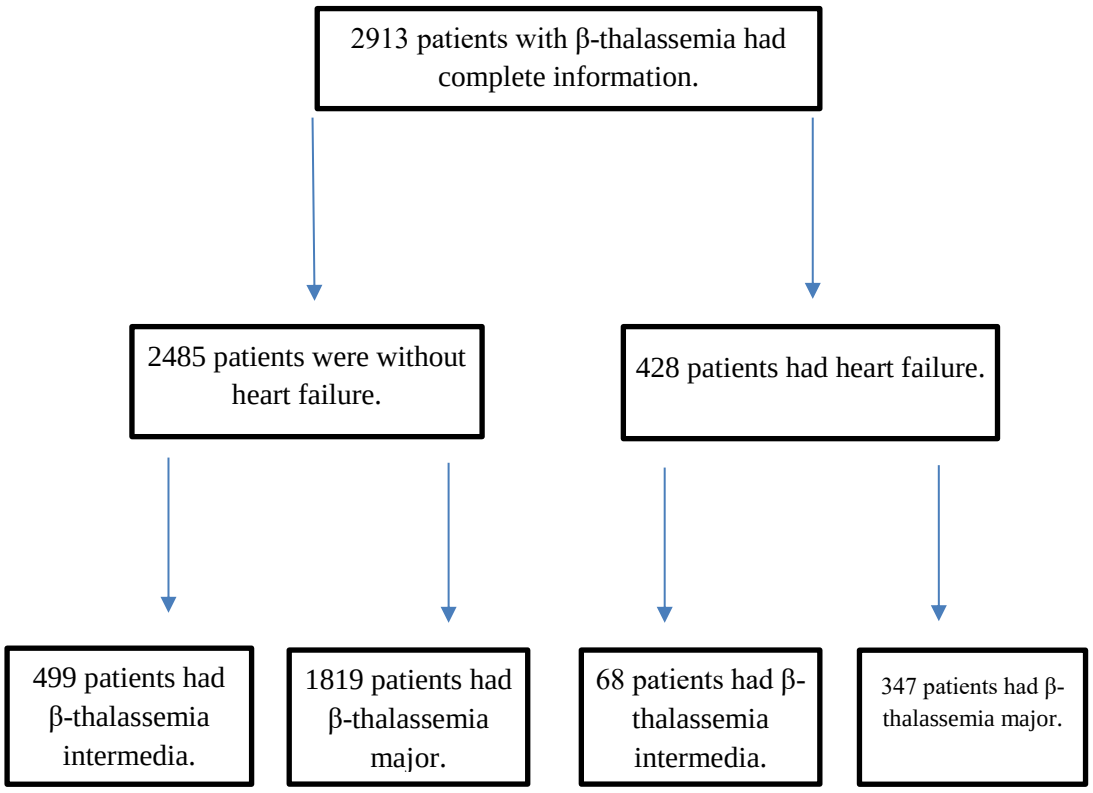
Congestive HF is due to a combination of systolic and diastolic dysfunction, but diastolic dysfunction is not very uncommon with a preserved left ventricular systolic function, especially in young patients.

Chronic HF due to myocardial hemosiderosis usually occurs during the second decade.

CONCLUSIONS

Despite advances in thalassemia management and patient survival management, cardiac complications are the most important causes of mortality in thalassemia patients. According to the results, some of the factors associated with the increased risk of HF in thalassemia patients can be more controllable. As a result, the appropriate and timely onset of blood transfusions and iron chelators, as well as long-life follow-ups, could lead to the early detection of cardiac involvement and the early treatment of the disease. For the prevention of iron accumulation in the body, chelation therapy should at least balance the iron received through transfusions and iron excretion. The development of classical HF indicates advanced disease with a poor prognosis. Intensive and fast chelation therapy in the acute phase is the choice treatment for patients.

All tests, including ferritin levels and liver iron concentrations, in conjunction with the conventional assessment of cardiac function via chest radiography, electrocardiography, and echocardiography, are necessary to predict patients' heart risk.



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