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COMPLICATIONS OF BETA-THALASSEMIA PATIENTS AND THEIR RELATED FACTORS IN IRAN

[1]Mahmoud Hajipour, [2]Maryam Soltani, [3]Rahimeh Najafifar, *[4]Shahab Rezaeian, [5]Sara Bistoon-beigloo, [6]Tannaz Valadbeigi, [7]Mohsen Shafiee, [8]Mehdi Sharafi, [9]Mehran Rezaei, [10]Farzaneh Mobasheri and [11]Ali Ghasemi

[1,2,3,6]Student Research Committee, Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[*,4]Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[5]Department of Clinical Biochemistry, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[7,9]Department of Nursing, School of Nursing & Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[8]Department of Disease Control, Deputy of Health, Fasa University of Medical Sciences, Fasa, Iran
[10]Department of Epidemiology, Fasa University of Medical Sciences, Fasa, Iran
[11]Student Research Committee, Department of Epidemiology, School of Health, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

Purpose: β-thalassemia is one of the most common hereditary diseases in the world. Frequent blood transfusions for symptomatic treatment of the disease minimize the associated complications such as ineffective hematopoises and anemia. However, iron overloading is caused by frequent blood transfusions leading to a variety of other complications such as liver, heart and endocrine disorders as well. The aim of this study was to determine the β-thalassemia associated complications and also other factors associated with the symptomatic treatment of this disease.
Methods: This cross-sectional study was conducted in Shiraz City, in 2014 enrolling 911 β-thalassemia patients from the southern of Iran. Data was collected from the patient's medical records and the analyses were conducted using bivariate logistic regression.
Results: The results showed that the most common complications are endocrine gland disorders (54.9 %), cardiovascular problems (18.6%), and infectious diseases (4.5 %). The risk of the endocrine complications in patients who had been administered to use two or more drugs was nearly 2-foldas compared to the patients who were on one drug. In patients whose serum ferritin levels were high, the risk of infectious diseases was approximately 2-fold when compared to those with low levels of serum ferritin. Based on our analyses, hemoglobin levels, ferritin levels, combined therapy and sex were related to the disease complications.
Conclusions: Overall, the results showed that in patients with high blood levels of ferritin, low hemoglobin level and patients who used 2 drugs or more, the risk of complications were significantly higher as compared to the other patients.

INTRODUCTION

Prevention and control of chronic non-communicable diseases is one of the main priorities of the health system and treating them is a health challenge as well (World Health Organization, 2013). These diseases cause greater financial and psychological problems for the patients and their health care system and they are life-threatening, severe and costly for treatment. One of the most common hereditary disorders is β-thalassemia in Iran. There are nearly two million carriers and an extensive spectrum of mutations in the gene encoding the beta-globin protein (Nozari *et al.,* 1995; Haghpanah *et al.,* 2014). The underlying mechanism of β-thalassemia is inherited deficiency of hemoglobin protein production, in which there is a complete or partial failure to synthesize beta-globin chains (Nozari *et al.,* 1995).

Corresponding author: Shahab Rezaeian,
Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

Regular blood transfusions are the most common method of treatment for normal growth and continuation of life in the β-thalassemia patients (Nozari *et al.,* 1995). In other words, the life of major β-thalassemia patients is dependent on regular blood transfusions and as a result, the accumulation of iron in various organs of the patients occurs. Liver, heart, pancreas, pituitary, parathyroid, and other organs are the sites of extra iron deposition. Accumulation of iron in the body leads to cell apoptosis and fibrosis, which result in multiple organ dysfunctions. Such organ dysfunctions manifest as cardiac insufficiency (Atiq *et al.,* 2006), liver disorders, hypogonadism (Moayeri and Oloomi, 2006), diabetes (Khalifa *et al.,* 2004), growth disorders, thyroid and parathyroid disorders (Najafipour *et al.,* 2008; Angelopoulos *et al.,* 2006), and also the highly important risk is the acquisition of blood-borne virus infections, particularly viral hepatitis and HIV (Mirmomen *et al.,* 2006). In this study, we evaluated the rates of cardiac and endocrine complications as well as blood-borne viral infections in β-thalassemia patients who medically treated with regular transfusions. Associations between the occurrence of these complications and serum ferritin levels and other epidemiological factors were also determined.

METHODS

This cross-sectional study was conducted in 2014 enrolling 911 β-thalassemia patients in the Dastgheyb Hospital for blood transfusion in Shiraz City, the south of Iran. All patients (911 individuals) with β-thalassemia diagnosis which have been visited and recorded in this hospital were included in this study. The patients were evaluated for their profiles and their retrospective information about their disease course. At the end of inclusion, two of the patients were excluded from the study because of their incomplete data. As β-thalassemia disease is a genetic defect, early diagnosis was performed in newborns and the patients were hospitalized for further treatments. As the diagnosis was confirmed, the patient was enrolled in the study and the variables were recorded over the time and information from their profiles was extracted and considered. The data of all patients based on census method were cross-sectionally extracted from patients' medical records using a predetermined checklist including age (calendar age at the study enrollment time), sex, education level, marital status (single or married), consanguinity, date of birth, date of death (if applicable), blood group, ferritin & hemoglobin level, blood transfusions, type of iron chelation drugs (deferrioxamine, deferiprone, exjade, desferal or esferal), type of β-thalassemia (major or intermedia), and accompanied diseases (heart failure, diabetes type 2, hypogonadism, thyroidism, parathyroidism, osteoporosis, HIV/AIDS, hepatitis B or C). Ferritin and hemoglobin levels were measured every six months and once a month, respectively. The average level of the last four times (except for two patients) was considered as the level of ferrritin and hemoglobin in further analyses for each patient.

Statistical Analysis

To investigate the association between demographic and epidemiological factors with complication and to estimate the adjusted odds ratio (OR) for complication, binary logistic regression analysis was performed.

All factors which were significant with a *P* value of < 0.2 on analysis were entered into a logistic regression to determine independent predictors of complication. A value of $P< 0.05$ was considered statistically significant. Data analyses were performed using SPSS software (version 19).

RESULTS

The distributions of complications in the thalassemia patients have been shown in Table 1.

Table 1. Distribution of complications in the beta-thalassemia patients

		No.	%	Total
Cardiac	Heart failure	169	18.6	18.6%
	Diabetes	125	13.7	
	Hypogonadism	261	28.7	
Endocrine	Thyroidism	41	4.5	54.9%
	Parathyroidism	233	25.6	
	Osteoporosis	312	34.3	
	AIDS	2	0.2	4.5%
Infectious	Hepatitis B	2	0.2	
	Hepatitis C	37	4.1	

The complications consist of endocrine complications including, 660 patients (54.9%), cardiac complications, including 169 patients (18/6%) and infectious diseases including 41 patients (4.5%). The most prevalent complications in the endocrine glands and infectious diseases were osteoporosis (34.3%) and hepatitis C (4.1%), respectively. Moreover, 389 of the patients (42%) underwent splenectomy due to frequent blood transfusion and also for prevention of stroke. The results of the crude and also adjusted analyses of endocrine-related effects of the variables have been shown in Table 2. There was a relationship between endocrine disease variables such as gender, marital status, consanguinity, and the type of thalassemia and the types of combination therapy in the crude analyses. After adjustment, the incidence of endocrine disorders in women (35%) was much higher than men [OR=1.35, 95%CI (1.03, 1.77)]. In patients consuming two or more than two drugs, the risk of the complications was more than patients consuming one drug [OR=1.98, 95%CI (1.48, 2.63)]. The results of crude and adjusted analyses of the variables associated with cardiac complications have been shown in Table 3.

The crude data were interpreted for a relationship between heart disease and gender, marital status, consanguinity, type of thalassemia, and the types of combination therapy. After adjustment, the risk of cardiac complications in men was 30% more than women [OR=0.70, 95% CI (0.49, 0.96)]. The ferritin and hemoglobin levels were also in relationship with heart disease. Thus, in patients who had higher serum ferritin levels the incidence of complications were 56% more than those who had lower serum ferritin levels. Also, patients with a hemoglobin level of greater than 9.5 g/dl (33%) had a lower risk of heart failure in comparison with patients who had a greater hemoglobin level [OR=0.67,95% CI (0.48, 0.94)]. The results of crude and adjusted analyses of the variables associated with infection complications have been shown in Table 4. In the crude analysis between the endocrine diseases with gender, marital status, consanguinity, type of thalassemia,

Table 2. Crude and adjusted odds ratio (OR) estimates of the different variables on endocrine complications in the beta-thalassemia patients

	Crude			Adjusted		
Endocrine	OR	95% CI	P value	OR	95% CI	P value
Sex						
Male	1	-	-	1	-	-
Female	1.36	(1.05, 1.77)	0.020	1.35	(1.03, 1.77)	0.028
Marital status						
Single	1	-	-	1	-	-
Married	1.07	(0.71, 1.63)	0.742			
Consanguinity						
No relation	1	-	-	1	-	-
Relationship	0.89	(0.68, 1.18)	0.428			
Type of thalassemia						
Intermedia	1	-	-	1	-	-
Major	0.83	(0.61, 1.11)	0.203			
Combined therapy						
One drug	1	-	-	1	-	-
Two or more	1.91	(1.44, 2.52)	0.001	1.98	(1.48, 2.63)	0.001

Table 3. Crude and adjusted odds ratio (OR) estimates of the different variables on cardiac complications in the beta-thalassemia patients

	Crude			Adjusted		
Cardiac	OR	95% CI	P value	OR	95% CI	P value
Sex						
Male	1	-	-	1	-	-
Female	0.67	(0.50, 0.93)	0.018	0.70	(0.49, 0.96)	0.029
Marital status						
Single	1	-	-	1	-	-
Married	1.04	(0.61, 1.79)	0.868			
Consanguinity						
No relation	1	-	-	1	-	-
Relationship	0.99	(0.71, 1.40)	0.971			
Type of thalassemia						
Intermedia	1	-	-	1	-	-
Major	0.81	(0.56, 1.17)	0.270			
Hemoglobin level (g/dl)						
<9.5	1	-	-	1	-	-
>9.5	0.65	(0.46, 0.91)	0.011	0.67	(0.48, 0.94)	0.022
Ferritin level (ng/mL)						
<2500	1	-	-	1	-	-
>2500	1.63	(1.16, 2.30)	0.005	1.56	(1.11, 2.19)	0.010
Combined therapy						
One drug	1	-	-	1	-	-
Two or more	0.96	(0.68, 1.36)	0.829			

Table 4. Crude and adjusted odds ratio (OR) estimates of the different variables on infectious complications in the beta-thalassemia patients

	Crude			Adjusted		
Infectious	OR	95% CI	P value	OR	95% CI	P value
Sex						
Male	1	-	-	1	-	-
Female	0.67	(0.36, 1.27)	0.223			
Marital status						
Single	1	-	-	1	-	-
Married	0.41	(0.10, 1.73)	0.227			
Consanguinity						
No relation	1	-	-	1	-	-
Relationship	0.93	(0.50, 1.75)	0.829			
Type of thalassemia						
Intermedia	1	-	-	1	-	-
Major	1.82	(0.80, 4.16)	0.270			
Hemoglobin level (g/dl)						
<9.5	1	-	-	1	-	-
>9.5	0.73	(0.39, 1.37)	0.329			
Ferritin level (ng/mL)						
<2500	1	-	-	1	-	-
>2500	1.98	(1.05, 3.72)	0.034	1.98	(1.05, 3.72)	0.034
Combined therapy						
One drug	1	-	-	1	-	-
Two or more	0.91	(0.45, 1.76)	0.777			

hemoglobin and serum ferritin levels and the types of combination therapy, the relationships were found. After matching, the relationship between the incidences of infection complications was observed with ferritin serum levels. Thus, the risk of infection disease in patients with more levels of blood ferritin was twice more than those whose blood ferritin levels were lower than 2500 (ng/mL), [OR=1.98, 95% CI (1.05, 3.72)].

DISCUSSION

In the present study, the most common complications of β-thalassemia were endocrine disorders (54.9 %), heart failure (18.6 %) and infections (4.5 %). In our study, the prevalence of endocrine complications was comparable with other studies (Charafeddine *et al.,* 2008; Zamani *et al.,* 2015). The most common endocrine complications were osteoporosis (34.3%) and hypogonadism (28.7 %) and also the most frequent infection complication was hepatitis C (4.1%). Unfortunately, due to the high cost and also due to the lack of proper facilities and osteoporosis diagnostic testing (DEXA: dual energy X-ray absorptiometry), a few studies in this regard are available. Among the reasons for the high incidence of this complication are more active bone marrow, iron overload, endocrine dysfunction and deferoxamine side effects. Due to the high incidence of this complication, it is recommended to consider the treatment of this complication seriously and try to reduce and improve the conditions of the patients by supporting them using various insurances (Borgna-Pignatti and Gamberini, 2011).

According to Low *et al*. study (Low *et al.,* 1997), the main reasons for the high prevalence of hypogonadism in the patients can be: GH and IGF1 levels reductions, growth hormone resistance, nutrition, zinc deficiency, iron overload, chronic hypoxia and the impact of deferoxamine on epiphysial plate growth. To reduce this effect, ferritin level should be reduced to less than 1500 (ng/ml). In addition, following up the patients for supportive treatment needed and we should teach them and their parents the compliance with treatment and daily food intake (Charafeddine *et al.,* 2008). Generally, the prevalence of endocrine complications in these patients is high and to prevent this complication, its risk factors (including age at onset of chelation therapy, low compliance with chelation therapy, splenectomy and severity of impairment in the gene encodes beta-globin) should be taken into consideration.

In general, due to extramedullary hematopoiesis, liver and spleen are enlarged in patients with thalassemia and some patients undergoing splenectomy at a very young age inevitably. In our study, 389 patients (% 42) underwent splenectomy (Haghpanah *et al.,* 2014; Cohen *et al.,* 2004). Hypospelinc patients are at risk of fulminate sepsis, which increases the risk of death to more than 50%. Moreover, after splenectomy platelet number increases and this may be a factor for thrombosis. Due to the risk of death in patients with portal vein thrombosis, splenectomy is recommended in certain cases and if a person with thalassemia underwent splenectomy due to hypersplinsim, increases in the needs for blood transfusions, or due to other causes, the patients should receive prophylactic therapy for portal vein thrombosis (Krauth *et al.,* 2008). Also, to delay splenectomy in these patients, reducing the deposition of iron is necessary using regular injections of chelation therapy. In examining the relationship between gender and the occurrence of endocrine complications, the risk of developing of this complication in women was 35% more than men. According to the study of Ansari *et al* the main reason for this increased risk is that the lower age of puberty in women than men. On the other hand, these complications began to develop and diagnose sooner in women. So, in this case, it is recommended to monitor girls more than boys and this complication is more serious in girls (Ansari *et al.,* 2008). A significant association was found between heart failure and gender, since the incidence of heart failure in men was more than women (OR=0.70,CI:0.46,0.96). Possible reasons for this relationship are: commitment of the women to medical recommendations and chelation therapy and the time of blood transfusions, which are consistent with the results of Borgna-Pignatti *et al*. (1998) and (Marsella *et al.,* 2011).

Furthermore, there was no significant relationship between gender and infectious complications, which are consistent with the results of (Mirmomen *et al.,* 2006). The relationship between ferritin levels and infectious complications was in such a way that the risk of developing these complications in patients with higher ferritin levels was twice than those patients with lower ferritin levels. Also the risk of developing heart failure in patients with higher ferritin levels was 56% more than the patients with lower ferritin levels. These results are consistent with the results of (Mirmomen *et al.,* 2006), Din (Din *et al.,* 2014) and (Borgna-Pignatti *et al.,* 1998). They reported that a high number of transfusions, increasing iron overload and also transfusion at lower ages are the causes of this relationship. The hemoglobin level was also associated with heart failure so that the risk of heart failure in the patients with lower hemoglobin levels was 33% more than the patients with more than the expected hemoglobin level. The reason of this relationship could be explained, as the in the hemoglobin level decreases the transfusion volume increases and as a result, more iron enters the body and complications of iron overload increases.

On the other hand, there wasn't any relationship between hemoglobin levels and the risk of infectious complications development, which is consistent with the result of (Mirmomen *et al.,* 2006). The need for blood transfusions in patients with hemoglobin levels greater than 9.5 (g/dl) the injected blood volumes are lower and also their transfusion intervals are longer, which help to reduce the complications of iron overload in these patients. Our investigation about the relationship between the number of drugs and endocrine complications showed that the risk of developing complications in patients consuming two or more drugs is nearly two fold as compared to the patients consuming one drug. The reason for this significant relationship in our study can be the long-term administration of two drugs or more. The use of combination drug therapy in emergency situations and in the short-term improves the condition. Although better caring of the patients, on time regular transfusions and using the appropriate iron controlling regimes, life expectancy of thalassemia patients increases and also the quality of life of these patients improves, however, these patients are still faced

with complications related to various organ dysfunctions, therefore; to improve the quality of life of these patients and reducing various complications, paying special attention to several factors such as comorbidities in these patients, poor compliance with chelation therapy, low socioeconomic status, the psycho-social support state of patients and their families to prevent mental health issues, behavioral problems and disease complications is necessary. Moreover, the attitude of health care provider should be in such a way that with proper planning the complications associated with blood transfusions be reduced so that the uncomplicated survival of these patients be improved.

Limitations

A potential limitation of this study should be noted. We conducted a cross-sectional study for using the data recorded. On the other hand, using the relationships between the various factors which associated with disease complications, however, prospective studies with reliable sources of data are the best designs to achieve the best results. Therefore, the quality and precision of our primarily investigation depended on the quality of the recorded data in the medical records. For overcoming these limitations and for the sake of accuracy of the collected data, we visited and interviewed with the patients with uncompleted profiles or the corresponding families.

Conclusion

Our study showed that in patients with high blood levels of ferritin, low hemoglobin level and patients who used more than one drug were significantly at higher risk of complications and other variables in the study were not significantly associated with complication development. Addressing the related factors would help health care providers and physicians to provide the best care and to improve the survival rate.

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Conflict of interest

The authors declare that there is no conflict of interest.

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