Pattern and clinical profile of thalassemia among pediatric patients attending the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen

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Background Thalassemia is a type of inherited anemia. Its management is complex and expensive, and requires a multiple-team approach. Optimal and sufficient clinical care is demanding.

Aim The aim of this study was to determine the magnitude, sex and age distribution, clinical profile, complications, investigation, and management of transfusion-dependent β-thalassemia major among Yemeni pediatric patients attending the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen as, to our knowledge, no similar previous study has been carried out in Yemen.

Patients and methods This was a prospective, cross-sectional, descriptive study carried out during the period from January 2015 to December 2016. A total of 109 Yemeni pediatric transfusion-dependent β-thalassemia major patients who attended the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen were included. Detailed assessment of history, clinical examination, investigations, treatment, and follow-up were performed for every patient. The data were collected from the medical records of the patients.

Results There was a slight male predominance (53.2%), with a male to female ratio of 1.14 : 1. Approximately 33% of the patients were in the age group 7–10 years, followed by the age group 3–6 years. The mean age of the cases was 7.68 ±5.8 years. Positive parent consanguinity was present (74.2%) and the majority (64.2%) were first-degree relatives. The best outcome of thalassemia was among those patients 1.7 years old or younger at the time of diagnosis and those patients 2 years old or younger at first blood transfusion. Earlier initiation of chelating therapy yielded better outcomes and reduced the mortality rate with a highly statistically significant difference. The usage of a combination of both oral chelation and subcutaneous iron chelation (iron pump) therapies led to a noticeably better outcome and reduced the mortality rate markedly. A proportional relation was detected between serum ferritin level and mortality among the cases, with a statistically significant difference. The complication rate was high (40.2%). The mortality rate was also high (27.5%). Cardiac dysfunction was the major risk factor of death among our thalassemic patients as about 60% of the deaths were because of cardiac complications, with a highly statistically significant difference.

Conclusion Increasing awareness of the morbidity and mortality of transfusion-dependent β-thalassemia major among pediatric Yemeni patients, with an emphasis on the great importance of premarital screening before marriage in Yemen, is mandatory. For better outcomes, routine investigations to detect early complications with proper treatment of the predisposing factors and complications are necessary.

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Introduction

Inherited hemoglobin disorders are emerging as a global public health concern. An estimated 320 000 babies are born each year with a clinically significant hemoglobin disorder [1]. Nearly 80% of these births occur in developing countries. Most conservative estimates suggest that at least 5.2% of the world's population (over 360 million) carry a significant hemoglobin variant and there are in excess of 100 million β-thalassemia carriers, with a global prevalence of 1.5% [1–3].

The inherited β-thalassemias are the most frequent single-gene disorders globally [1]. β-Thalassemia major is the most common chronic hemolytic anemia among children and adolescents worldwide [4]. β-Thalassemia is most prevalent in certain malaria-prone parts of the world including Africa, all Mediterranean countries, the Middle East, the Indian subcontinent, and Southeast Asia [1,5–7]. The high prevalence in the Middle East can be attributed to the high prevalence (25–60%) of consanguineous marriages [8].

About 60 000 new patients are born annually with thalassemia worldwide [3]. Because of the high rate of international migration, thalassemias are spreading to nonendemic parts of the world. According to the

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Thalassemia International Federation, only about 200 000 patients with thalassemia major are alive and registered as receiving regular treatment around the world [9].

In Egypt, in 2009, El-Beshlawy and Youssry [10] reported that β-thalassemia is the most common type, with a carrier rate varying from 5.3 to 9% or more in different governorates of Egypt. Many studies indicate that thalassemia is common in the Gulf region such as Bahrain (18% α-thalassemia and 11% β-thalassemia) [11], Oman (6% α-thalassemia and 5.3% β-thalassemia) [12], UAE (3% α-thalassemia and 2.40% β-thalassemia) [13], Qatar (28% α-thalassemia and 17% β-thalassemia) [14], and Jordan (3.3% α-thalassemia and 3.5% β-thalassemia) [15].

Thalassemia is also common in other Arab countries such as Libya (5% α-thalassemia and 4% β-thalassemia) [16], Tunisia (4.8% α-thalassemia and 4.4% β-thalassemia) [17], and Algeria (9% α-thalassemia and 3% β-thalassemia) [18].

Yemen is a poor country, with a population of about 24 million, where hereditary hemoglobinopathies are common and represent a significant health problem. It has been shown that the prevalence of thalassemia was reported to be 13% (8.6% for α-thalassemia and 4.4% for β-thalassemia traits) in Sana'a city [19].

Standard thalassemia management involves a multi-disciplinary approach involving an array of specialties including pediatric hematology, pediatric hepatology, infectious disease, transfusion medicine, endocrinology, cardiology, dentistry, dieticians, psychiatry, and social work along with a robust blood bank system and infrastructure [20]. Treatments available for thalassemia patients are regular blood transfusion, iron chelation therapy in an attempt to prevent iron overload and the judicious use of splenectomy in cases complicated by hypersplenism, and hematopoietic stem cell transplantation [21].

Regular blood transfusion programs and chelation treatment have considerably improved the survival of patients with thalassemia. However, a side effect of chronic transfusion therapy is secondary iron overload, which adversely affects the functions of the heart, liver, and other organs, causing severe morbidity, and shortens the life expectancy [4]. The age of cardiac death depends primarily on access to transfusions and chelation. In transfused, but unchelated patients, the typical age at death is 10 years, primarily of cardiac causes [22].

Several treatments could become available for the future management of thalassemia. These could involve the use of chelation therapies for increasing iron excretion, chelation therapies for inhibiting iron absorption, chelation therapies for iron redistribution, selected diets with lower and less absorbable forms of iron, the use of regulators of hepcidin, ferroportin, and other proteins of iron metabolism involved in the transport of iron, activators of Fetal hemoglobin production (HbF) production, and combinations of such treatments [23–26].

The curative treatment is bone marrow transplantation, which is expensive; thus, prevention is a cost-effective strategy to reduce the burden of the thalassemia patients on families and to manage a sustainable healthcare system [27].

A primary preventive program is based on carrier (heterozygous) detection and counseling to discourage marriage between carriers [28]. Overall, premarital screening (PMS) for thalassemia and other preventable genetic diseases is widespread in many parts of the world [29]. PMS has yet to be established in the countries where consanguineous marriage rate is high (40%); more than 85% of which are between first cousins and traditional marriages, which may make its acceptance difficult. Thus, PMS for inherited diseases is an important method to minimize their occurrences among high-risk populations and to reduce social, emotional, and financial burden on the family and society. PMS has been successful in many parts of the world [30].

β-Thalassemia major is one of the important hemoglobinopathies in Yemen and with its clinical severity, it is considered a major health problem in Yemen. The prolonged instability in our country because of the current war has led to an obvious deterioration in the health services in general with the absence of essential drugs such as chelating drugs specifically. These problems are the cause of major tragedy among Yemeni patients.

There have been no recent good-quality researches on the situation of thalassemia in Yemen to the best of our knowledge; thus, this cross-sectional descriptive study aimed to determine the demographic characteristics of the Yemeni pediatric transfusion-dependent β-thalassemia major patients, the relationship between the outcome among the studied cases and their age, serum ferritin level, and type of therapy, and the common complications of blood transfusion that tend to be exaggerated, especially among poor individuals, who unfortunately make up the majority of patients.

Patients and methods

This cross-sectional descriptive study was carried out on 109 Yemeni pediatric transfusion-dependent β-thalassemia major patients out of 399 patients who were registered at the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen during the period from January 2015 to December 2016. These centers are located in the following Yemeni governorates: Sana'a, Taiz, Al-Hudaydah, and Hadhramaut.

All patients who were clinically diagnosed with transfusion-dependent β-thalassemia major, whether alive or died because of the disease itself, its complications, or therapy complications, were included in this study. Patients were of both sexes and from all age groups.

Transfusion-dependent β-thalassemia major Yemeni patients who had other debilitating diseases not related to thalassemia or those who were diagnosed with transfusion-dependent β-thalassemia and died because of other diseases were excluded from the study. This was detected by assessment of history, clinical examination, and appropriate laboratory investigations. The families of the patients who were difficulty to reach, as they do not have a telephone line where they live, were also excluded from the study.

One hundred and nine Yemeni pediatric transfusion-dependent β-thalassemia major patients (30 dead cases and 79 live cases) were involved in the study. The data were collected from the medical records of the studied cases using a questionnaire that included the following variables: demographic characteristics of the patients (age, sex, residency, consanguinity of parents, etc.), age at the time of diagnosis, types of therapy (blood transfusion and chelating therapy), associated diseases (heart disease, liver disease, renal disease, infectious disease, and endocrine disease), investigations, complications, etc. Telephone calls and interviews with the studied cases and their parents or relatives were conducted when the medical record of any of the cases was incomplete.

The studied cases were divided into five age groups: less than 3, 3–6, 7–10, 11–14, and more than 15years.

Statistical analysis

The analysis of data was carried out using the SPSS (version 21; SPSS Inc., Chicago, Illinois, USA). The results were properly summarized and presented as frequency, percentage, means, and SD. The population was compared in terms of demographical data using the χ^2-test. Data were presented in the form of tables and graphs. Categorical data were compared using the χ^2-test procedure in the form of tables and provides tests and measures of association. Statistical significance was considered at a *P*-value less than 0.05.

Results

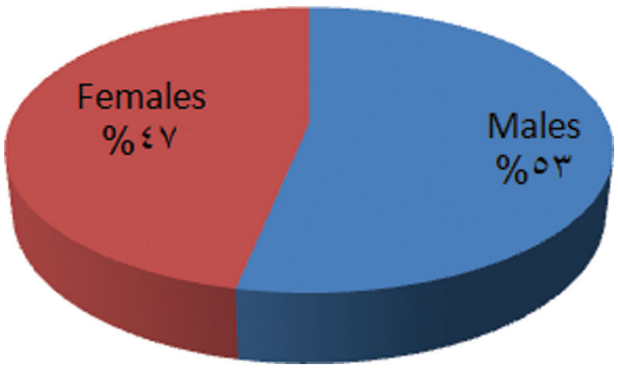
In this cross-sectional descriptive study, 109 Yemeni pediatric transfusion-dependent β-thalassemia major patients (30 dead cases and 79 live cases) who attended and were registered at the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen during the period from January 2015 to December 2016 were involved.

Figure 1 shows the sex distribution of the studied cases. There was a slight male predominance. Of the total cases, males accounted for 53.2% (58 cases), whereas females accounted for 46.8% (51 cases). The male to female ratio was 1.14 : 1 (Fig. 1).

Figure 2 shows the age distribution among the studied cases. The studied cases were divided into five age groups. About one-third of the studied cases (36 cases; 33.03%) were in the age group of 7–10 years, followed by the age group 3–6 years (23 cases; 21.1%), the age group 11–14 years (22 cases; 20.2%), and the age group 15 years and above (15 cases; 13.8%). The least presenting age group was less than 3 years (13 cases), representing only 11.9% of the total cases. The mean age of the studied cases was 7.68±5.8 years.

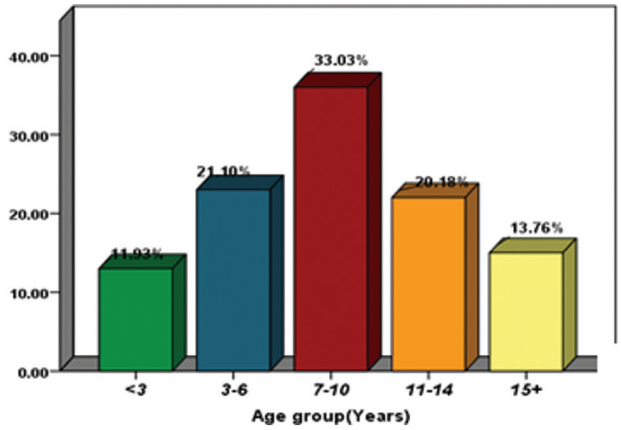
Figure 3 shows that positive parent consanguinity was found in around two-third of the cases studied (81 cases; 74.2%). The majority of them (70 cases; 64.2%) were first-degree relatives, whereas only 11 (10.1%) cases were second-degree relatives. One-third of the cases (28 cases; 25.7%) had no parental consanguinity (Fig. 3).

Figure 1



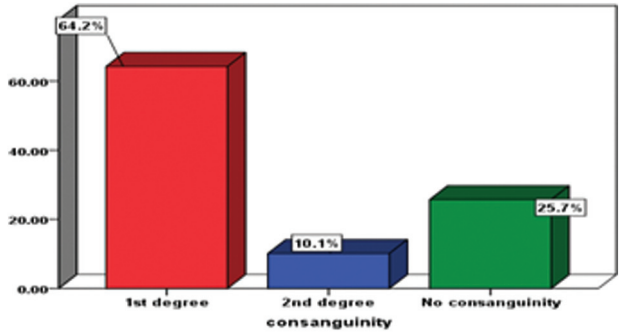
Sex distribution among the studied cases.

Figure 2



Age distribution among the studied cases.

Figure 3



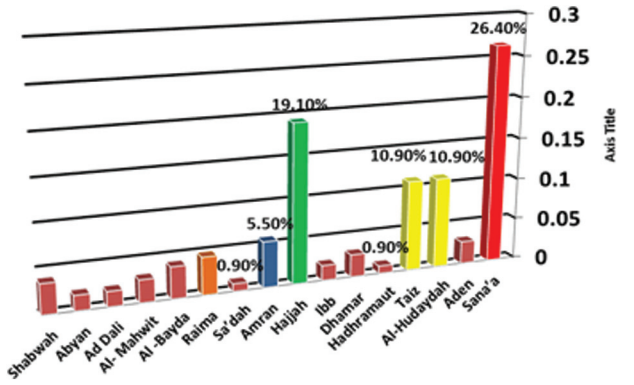
Parent consanguinity among the studied cases.

Figure 4 shows the residential distribution of the studied cases. The majority of our studied cases were from Sana'a (the capital of Yemen) (29 cases; 26.4%) and Hajja (21 cases; 19.1%). This was followed by Al-Hudaydah and Taiz, each representing 10.9%, Amran (5.5%), Rima (4.5%), Al-Bayda (3.8%), and Shabwa (3.6%). Aden, Al-Mahwit, and Dhamar each represented 2.7% of the total studied cases. Each of Abyan and IBB were represented 1.8% of the cases. Sa'da and Hadhramaut each represented only 0.9% of the total studied cases.

Figure 5 shows the investigations among the studied cases. The main investigations that our thalassemic patients underwent were determination of the levels of serum ferritin (64.2%), followed by liver function test (35.8%) and echocardiography (26.6%).

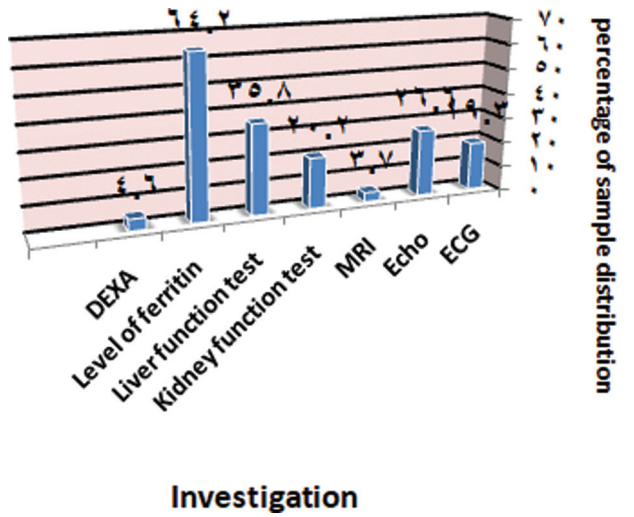
Table 1 shows the relationship between the outcome of the studied transfusion-dependent β-thalassemia major cases and their age at the time of diagnosis and at first blood transfusion. In terms of age at the time of diagnosis, the majority of the studied cases (61.5%) were 1.7 years or younger

Figure 4



Residence distribution among the studied cases.

Figure 5



Investigations among the studied cases.

at the time of diagnosis, whereas 38.5% of the studied cases were more than 1.7 years at the time of diagnosis.

The outcome was better among those aged 1.7 years or less as 85% of these cases were alive, and death occurred in only 14.9%, whereas at age more than 1.7 year, death occurred in nearly half of these cases (42%). Thus, there was a statistically significant difference between the age at the time of diagnosis and the outcome of the disease (P=0.001).

In terms of the age at the time of first blood transfusion, the majority of our studied transfusion-dependent β-thalassemia major cases (57.8%) were started on blood transfusion at the age of 2 years or less, whereas 13.8% of the cases were started on blood transfusion between 3 and 6 years of age, and 0.9% at age more than 6 years.

Table 1 Relationship between the outcome of the studied transfusion-dependent β-thalassemia major cases and their age at the time of diagnosis and at first blood transfusion

Age grouping (years)	Outcome of cases [*n* (%)[a]]		Total	χ^2	*P*-value
	Alive	Dead			
At the time of diagnosis					
≤1.7	57 (85)	10 (14.9)	67	11.106	**0.001****
<1.7	22 (52.4)	20 (47.6)	42		
Started first blood transfusion					
≤2	63 (72.4)	24 (27.6)	87	6.072	**0.048****
3–6	15 (83.3)	3 (16.7)	18		
6+	1 (25)	3 (75)	4		

[a]The percentage was calculated from the horizontal total; **$P<0.05$ is considered statistically significant and the bold values are less than 0.05.

Table 2 Relationship between the outcome of the studied cases and age when first chelating therapy was initiated

Age (years) when first chelating therapy was initiated	Outcome [*n* (%)[a]]		Total [*n* (%)[b]]	χ^2	*P*-value
	Alive	Dead			
>3	13 (100)	0 (0)	13 (19.7)	9.999	0.019*
3–6	16 (90)	3 (10)	19 (28.9)		
7–10	20 (83.3)	4 (16.7)	24 (36.5)		
11+	5 (50)	5 (50)	10 (15.2)		
Total	54 (81.8)	12 (18.2)	66 (100)		

[a]The percentage was calculated from the horizontal total; [b]The percentage was calculated from the vertical total; *$P<0.05$ is considered statistically significant.

The outcome was better among those between 3 and 6 years of age, and most cases who were 2 years old or younger were alive, representing 83.3 and 72.4% of the age group, respectively, whereas at age more than 6 years, the outcome was poor as death occurred in around two-thirds of them (72.4%). There was also a statistically significant difference between age at first blood transfusion and the outcome of the disease (P=0.048).

The best outcome in our transfusion-dependent β-thalassemia major cases was that among patients who were 1.7 years old or younger at the time of diagnosis and/or those who were 2 years old or younger at the time of first blood transfusion.

Table 2 shows the relationship between the outcome of the studied cases and their age when the first chelating agent was initiated. Around 60.6% of the cases (66 cases) had received chelating therapy. Around 81.8% of them (54 cases) remained alive, whereas 18.2% (12 cases) died.

The majority of the cases (36.5%) were in the age group 7–10 years when the first chelating agent was initiated. Two-third of these patients (83.3%) remained alive and 16.7% died.

We found that earlier initiation of chelating therapy in 19.7% of the cases at age less than 3 years led to the best outcome of the cases, with no mortality. Furthermore, out of the 19 (28.9%) cases in whom the first chelating therapy was started between 3 and 6 years of age, 16 (90%) patients remained alive and only 10% of these patients died. The mortality rate was high (50%) among those in whom the first chelating therapy was started at the age of 11 years and older. Thus, earlier initiation of chelating therapy led to better outcomes and reduced the mortality rate, with a highly statistically significant difference (P=0.0190).

Table 3 shows the relationship between the outcome of the studied cases and the type of iron chelation therapy that they received. Single-chelation therapy with Exjade (deferasirox tablets) was used in only 16 (24.2%) of the total cases who received chelation therapy; the majority of them (13 cases; 75%) remained alive and 25% died.

Single-chelation therapy with Desferal was administered in 20 cases (30.3%); two-third of these patients (13 cases; 65%) remained alive and 35% (seven cases) died.

Combined chelation therapy using both Exjade and Desferal was administered in 30 cases, representing nearly half (45.5%) of the total cases who received chelation therapy; the majority (29 cases; 96.7%) of them remained alive and only one (3.3%) patient died. Combined therapy was indicated for cases with poor compliance to parenteral therapy, cases with no response to monotherapy, and some cases with iron-overload cardiomyopathy for the rapid removal of excess cardiac iron.

The usage of a combination of both oral and parenteral chelation therapies led to a noticeably better outcome and the mortality rate was markedly reduced to 3.3% in comparison with the mortality rates of 25 and 35% among patients receiving single-chelation therapy with Exjade and Desferal, respectively.

Table 4 shows the relationship between the outcome of the studied cases and their serum ferritin levels. The serum ferritin level was between 1000 and 3000 ng/ml in nearly half of the studied cases (48.4%), between 3000 and 6000 ng/ml in 22.6% of the cases, between 6000 and 9000 ng/ml in 17.7% of the cases, less than 1000 ng/ml in 8.1% of the cases, and more than 9000 ng/ml in 3.2% of the cases.

We found that the highest mortality rate (63.6%) was among those with serum ferritin levels between 6000 and 9000 ng/ml and represented 50% of the dead patients studied. The mortality rate was 21.4%, about 40% less among those with lower levels of serum ferritin between 3000 and 6000 ng/ml, which further decreased to half (10%) among those with lower serum ferritin levels between 1000 and 3000 ng/ml and to zero among those with the lowest serum ferritin levels >)1000 ng/ml(, with a highly statistically significant difference (P=0.004). The difference between the mortality rate of 63.6% among those with serum ferritin levels between 6000 and 9000 ng/ml (11 cases) and the mortality rate of 50% among those with serum ferritin levels more than 9000 ng/ml (two cases) was not statistically significant because of the huge difference in the number of cases in each. This indicates that high serum ferritin level is a risk factor for early death and at lower levels of serum ferritin, the mortality rate decreased in proportion.

Table 3 Relationship between the type of iron-chelation therapy used and outcome among the studied cases

Types of iron chelation therapy	Outcome [*n* (%)[a]]		Total [*n* (%)[b]]
	Alive	Dead	
Exjade	12 (75)	4 (25)	16 (24.2)
Desferal	13 (65)	7 (35)	20 (30.3)
Exjade+Desferal	29 (96.7)	1 (3.3)	30 (45.5)
Total	54 (81.8)	12 (18.2)	66 (100)

[a]The percentage was calculated from horizontal total; [b]The percentage was calculated from vertical total.

Table 5 shows the relationship between the outcome of the studied cases and the complications of blood transfusion and iron overload. It was detected among 45 cases, representing 41.3% of the total studied cases. The most common complication was heart disease mostly in the form of cardiomyopathy (19.3% of the total cases) (around half of the complicated cases; 46.7%), followed by liver disease (11%), nephropathy (6.4%), and infection (hepatitis) (3.7%).

There was a statistically significant relationship between the outcome of the cases and the complications of blood transfusion and iron overload as the mortality rate was high (85.7%) among patients with complications of heart diseases, with a high statistically significant difference (P=0.000).

Discussion

This cross-sectional descriptive study was carried out on 109 Yemeni pediatric transfusion-dependent β-thalassemia major patients (30 dead cases and 79 live cases) who were registered at the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen during the period from January 2015 to December 2016.

A slight male predominance was detected among our studied cases as males represented 53.2% of the total studied cases, with a male to female ratio of 1.14 : 1. Our result is in agreement with a similar study carried out in Bangladesh, in 2017, which reported a male to female ratio of 1.26 [28]. A similar result was reported in an Indian study, in 2016, which found that 53.3% of their cases were males and 46.6% were females [31]. Zamani *et al.* [32] reported that among their studied

Table 4 Relationship between outcome of the studied cases and their serum ferritin level

Serum ferritin levels (ng/ml)	Outcome [*n* (%)[a]]		Total [*n* (%)[b]]	χ^2	*P*-value
	Alive	Dead			
>1000	5 (100.0)	0 (0)	5 (8.1)	15.651	0.004*
1000–3000	27 (90)	3 (10)	30 (48.4)		
3000–6000	11 (78.6)	3 (21.4)	14 (22.6)		
6000–9000	4 (36.4)	7 (63.6)	11 (17.7)		
9000+	1 (50)	1 (50)	2 (3.2)		
Total	48 (77.4)	14 (22.6)	62 (100)		

[a]The percentage was calculated from the horizontal total; [b]The percentage was calculated from the vertical total; *P<0.05 is considered statistically significant.

Table 5 Relationship between the outcome of the studied cases and complications of blood transfusion and iron overload

Complications of blood transfusion	Outcome [*n* (%)[a]]		Total [*n* (%)[b]]	χ^2	*P*-value
	Alive	Dead			
Heart disease	3 (14.3)	18 (85.7)	21 (19.3)	16.102	0.000*
Liver disease	6 (50)	6 (50)	12 (11)	1.529	0.294
Endocrinopathy	1 (100)	0 (0)	1 (1.8)	4.902	0.084
Nephropathy	3 (43)	4 (57)	7 (6.4)	1.305	0.356
Hepatitis C	2 (50)	2 (50)	4 (3.7)	4.902	0.084

[a]The percentage was calculated from the horizontal total; [b]The percentage was calculated from the vertical total; *$P<0.05$ is considered statistically significant.

thalassemic patients in Hamdan province in Iran, 54.9% were males. In addition, Bejaoui and Guirat [33] found that in Tunisia, 55.4% of male patients were thalassemic, whereas 44.5% were female patients.

Studies from the West, Mediterranean, and Middle East have shown a slightly higher incidence of thalassemia among male children [34–38]. A Lebanese study carried out in 2005 reported a slightly higher percentage of males (57%) among their thalassemic children [39].

In the literature, other previous Indian studies have reported a further higher male preponderance of up to 68% [40] and 69.5% [41]. Shah *et al.* [42] found that in western India, 62% (88 cases) of their studied cases with thalassemia were males, whereas 38% (54 cases) were females. In 2015, a higher male to female ratio (2.5 : 1) was reported among Indian children with thalassemia, with 71.4% being males [43]. In addition, in 2016, a higher male predominance was reported among Saudi children with thalassemia as 70% were males, with a male to female ratio of 2.3 : 1 [44].

Our result is not in agreement with a similar study carried out in Hong Kong that found that the male to female ratio was equal among their studied thalassemic cases [45]. In addition, in 2013, a similar study was carried out in Dubai and showed no significant difference in the incidence of thalassemia between both sexes as 50.5% of their patients were males [46]. This could be explained by the fact that males are always overprotected and received more care in these countries.

The mean age of our studied cases was 7.68±5.8 years. About one-third (33%) of the cases were in the age group 7–10 years, followed by the age group 3–6 years. Our result is in agreement with Bejaoui and Guirat [33] reporting a median age of 10.7 years among thalassemic patients in Tunisia.

In contrast to our results, in 2016, a lower mean age of 3.7 years was reported in a similar study carried out in India [31]. In addition, the mean age in an Indian cohort study was 17.2±19.9 months, with 50% being diagnosed within the first year of life [43]. Kattamis *et al.* [47] noted age at presentation to be 13.1 (2–36) months. Cao and Galanello [48] reported the mean age of children with thalassemia to be 8.4±9.1 months. Modell and Berdoukas [49] reported 60% of their patients had presented clinically in the first year of life, with the mean age being 6 months. This could be explained to the late detection of the disease in Yemen because of the low level of community awareness of the disease as well as the poor socioeconomic level and fewer available facilities to seek medical advice.

However, a comparably higher mean age of the pediatric thalassemic patients (15.4 years) was reported in United Arab Emirates in 2013 [46]. A higher median age of the pediatric thalassemic patients was also reported in Hong Kong cohorts (15.5 years) and Iranian cohorts (15.2 years), and a much higher median age in North America cohorts (20 years) [45,50–52].

Positive parent consanguinity was found in around two-thirds of our studied cases (74.2%). The majority of them (64.2%) were first-degree relatives. This can be explained by the fact that thalassemia is transmitted in an autosomal recessive manner and a high consanguinity rate is a distinguishing feature of the disease. In addition, the prevalence of thalassemia is especially high in countries where there are marriages between closely related families [53]. A comparably high consanguinity rate (73.7%) was reported by Zamani *et al.* [32] among parents of pediatric thalassemic patients of the Balouch population in Iran. Similarly, in Tunisia, the geographic distribution of thalassemia in 2013 as reported by Bejaoui and Guirat [33] showed that thalassemia is highly concentrated in small towns, particularly in the western part of Tunisia, where there are marriages between close relatives, with a consanguinity rate of 75.3% among the patients' parents. Similarly, the rate of consanguinity among the parents of Iranian thalassemic patients living in Hamadan Province was 67.4% [54]. In 2005, a Lebanese study found a high

consanguinity rate (63%) among their thalassemic cases [39].

A comparably lower consanguinity rate (53%) was detected in western India in 2010 as Shah *et al*. [42] reported that the Muslim patients with thalassemia in their study were a result of a consanguineous marriage. In Shiraz city, Iran, Asadi-Pooya and Doroudchi [55] reported that 49.5% of thalassemic patients were a result of cousin marriages. In 2016, consanguineous marriage was detected in 26.6% of the parents of thalassemic Indian children [31].

The previous considerably high consanguinity rate among thalassemic patients' with some variations may be explained by several reasons, mainly, lack of knowledge of the increased risk of β-thalassemia after familial marriages among populations, especially among young individuals. Thus, to improve the situation, public awareness of thalassemia is of great importance and should be taught in periodic sessions.

In our study, the prevalence of transfusion-dependent β-thalassemia major was the highest (26.4%) among cases living in Sana'a (the capital city). This may be explained by the large migration flows from other towns of Yemen to the capital; thus, it accommodates many families from almost all regions of Yemen. In addition, the high altitude of Sana'a city, with low oxygen tension, leads to greater clinical severity in children with hemoglobinopathies because they cannot tolerate hypoxia like healthy individuals living at high altitude. Finally, the presence of the main center of the Yemeni Society of Thalassemia and Genetic Blood Disorders in Sana'a makes it easily for the patients living in Sana'a and nearby districts to reach medical care. Similarly, Bejaoui and Guirat [33] noticed that the large migration flows from the western towns of Tunisia to the capital contributed toward the higher prevalence of thalassemia in Tunisia.

Hajja was the second town in Yemen that had a high prevalence of thalassemia (19.1%). This could be attributed to the early appearance of clinical manifestations of the disease, leading to seeking of medical advice because of the high altitude, with low oxygen tension, the high-density population in Hajja, as well as the high rate of family marriages in the Hajja population. These results reflect the urgent need for community awareness and mandatory screening programs in the high-risk areas.

There is a disparity between rural and urban settings in terms of the availability of primary care services. There are only health centers/houses in rural areas and access to healthcare is difficult for rural residents. Zamani *et al*. [32] reported that 66.2% of their studied thalassemic patients in Hamdan province in Iran were from urban areas [32].

Our result is not in agreement with the Lebanese study that reported that thalassemia is homogeneously distributed all over Lebanon [39].

The main investigation that was carried out for our thalassemic patients was determination of the level of serum ferritin (64.2%), followed by a liver function test (35.8%).

There was a statistically significant difference between the outcomes of the studied cases and their age at the time of diagnosis (P=0.001) and their age at first blood transfusion (P=0.048). The best outcome of transfusion-dependent β-thalassemia major was among those patients 1.7 years or younger at the time of diagnosis and those patients 2 years or younger at first blood transfusion. This indicates that early diagnosis and early initiation of blood transfusion decrease the effect of the risk factors that cause early death. This result is similar to a study carried out in Iran, in 2005, which indicated decreased survival in proportion with increasing age in terms of time of diagnosis and receiving the first blood transfusion [56]. In addition, a similar study carried out in Saudi Arabia, in 2010, reported that the outcome in β-thalassemia major worsens with late onset of diagnosis and initiation of blood transfusion [57].

In our study, around 60.6% (66 cases) of the total cases studied (66 cases) had received iron chelation therapy, of whom 81.8% remained alive and 18.2% died. The remaining cases (39.4%) had not received any iron chelation therapy. This may be explained by several reasons, mainly lack of knowledge, difficulties in follow-up because of the low income of the concerned population, unavailability of chelators in some hospitals in our country, and poor compliance among some of the studied patients. Because of the high cost of the transfusions and chelating drugs, most of the thalassemia patients in developing countries are left to die untreated [58]. Our result is in agreement with Shah *et al*. [42], who found that 67% of their studied thalassemic patients were receiving some form of chelation therapy [42].

The local manufacture of cheaper formulations for chelation therapy in developing countries, such as India, Thailand, and Iran, has markedly reduced the

cost of chelating drugs, and a noticeable increase in the number of patients receiving chelation therapy in these countries was reported [59,60]. In addition, a comparably higher percentage of patients receiving chelation therapy (87.2%) was reported, in Tunisia, by Bejaoui and Guirat [33]. A comparably lower percentage of patients receiving chelation therapy (47%) was reported in Bangladesh in 2017 [28].

The optimal age for initiating iron chelation therapy in patients with thalassemia remains uncertain, although in theory it should begin as early as possible to prevent growth and developmental defects. Guidelines from the Thalassemia International Federation recommend that chelation therapy is initiated when serum ferritin levels reach ~1000 ng/ml, which usually occurs after the first 10–20 transfusions or around 2–3 years of age [61,62].

The majority of our studied cases (43.9%) were in the age group 7–10 years at the time of initiation of chelating agent therapy, whereas only 19.7% of the cases were younger than 3 years, which means that initiation of chelation therapy in our country mostly started at much later ages comparable with the optimal age advised by the Thalassemia International Federation (2–3 years) [61]. The delayed age at the time of initiation of chelating agent therapy in nearly half of our cases could be explained by the high rate of illiteracy in Yemen; hence, the ignorance to the importance of seeking medical advice early; also, the high poverty rate plays a role in seeking medical advice late (until the condition deteriorations and/or complications appearances) among educated individuals.

The mortality rate was high (50%) among those who started their first chelating therapy at the age of 11 years and older and was about 21.4% among those in whom the first chelating therapy was started between 7 and 10 years of age, whereas no mortality was detected among those in whom the first chelating therapy was started at the age of less than 3 years. Therefore, we found that earlier initiation of chelating therapy yielded better outcomes than late initiation and reduced the mortality rate with a statistically significant difference (P=0.0190).

Our result is very close to a similar Italian study that reported a statistically significant relation between early age at the time of initiation of chelating therapy and better outcome of the cases (P=0.019) [63]. In addition, a similar study carried out by Bejaoui and Guirat in Tunisia [33] reported that only a third of their thalassemic patients received chelation therapy before they had completed their third year and the remaining cases at later ages and the mean patient age at onset of the oral chelating treatment was 17 years (12–18 years).

Desferrioxamine has been the standard drug for iron chelation therapy [64], although a subcutaneous infusion negatively affects patient compliance [65]. In addition, oral chelating agents are also very expensive and the vast majority of patients cannot afford it, especially those living in developing countries [58,66–68]. The oral iron chelators, deferiprone and deferasirox, are effective in reducing iron burden, whereas at the same time, they improve compliance and patients' quality of life [69]. In 2010, Galanello *et al.* [70] reported that combinations of one oral chelator with deferoxamine have been used to increase the efficacy and induce negative iron balance in some patients with severe iron overload.

In our study, in addition to blood transfusion, a combination of both oral chelator deferasirox (Exjade) and parenteral deferoxamine has been used in nearly half (45.5%) of the chelated cases. Combined therapy was indicated for cases with poor compliance to parenteral therapy, cases that showed lack of response to monotherapy, and some cases with iron-overload cardiomyopathy for the rapid removal of excess cardiac iron. Single chelation therapy with Desferal and Exjade has been used in only 30.3 and 24.2% of the chelated cases, respectively.

The mortality rate among those treated with monotherapy was 25% among Exjade users, which is lower than that among Desferal users (35%). This result is in agreement with a study carried out in Saudi Arabia that reported that the majority of complicated patients were on nonoptimal chelation therapy and noncompliant [56]. Similarly, other studies carried out in Hong Kong [45] and Italy [63] found that Exjade therapy reduced the mortality because of its simplest oral administration. A study carried out in Lebanon also reported that including the oral chelator in the therapeutic plan protects against mortality [39].

In comparison, the majority (96.7%) of those who received the combination chelator remained alive and the mortality rate among these patients was only 3.3%. Thus, the usage of a combination of both oral and pump chelation therapies led to a noticeably better outcome and reduced the mortality rate markedly. This could be explained by the fact that the coadministration of deferoxamine and any oral chelator exerted a favorable and progressive effect of decreasing both plasma non-transferrin-bound iron (NTBI) that was not observed previously with either deferoxamine or

oral chelator as single agents [71]. The decrease in NTBI following the administration of oral chelators in patients concurrently infused with deferoxamine suggests that oral chelator accesses NTBI pools unavailable to deferoxamine alone [72]. This provides further evidence for the additive effects of oral chelator and deferoxamine. These results show an interested mechanism of action as synergistic removal of NTBI by combined oral chelators has also been observed [73].

In agreement with our study, the efficacy of combined chelation therapy with deferoxamine and oral chelator therapy has been shown in several studies [74–78]. In 2009, Taher *et al*. [79] reported the Egyptian experience, which showed the high efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with β-thalassemia who had been treated with previous monotherapy or combination therapy with deferoxamine and/or deferiprone: in the ESCALATOR study. In addition, the combination of deferasirox and deferoxamine has also been used both in the preclinical and in the clinical setting with encouraging results by Otto-Duessel *et al*. [80] and Jetsrisuparb *et al*. [81].

Our result is in agreement with the International Committee on Chelation protocol, which reported that selected combinations of deferoxamine and any oral chelating agent could be used as a first-line treatment not only for the rapid removal of excess cardiac iron in cases of iron-overload cardiomyopathy in thalassemic patients but also in the rapid clearance of liver-iron overload [82–86]. The introduction of combinations of deferoxamine with deferasirox increases the prospect of more effective and less toxic therapies for thalassemia in comparison with monotherapies [68,87–90]. In addition, a similar study carried out by Hajipour *et al*. [91], in Iran, found that the combination therapy of iron chelators used among their studied thalassemic cases was associated with a 70% lower risk of mortality.

In contrast to our study, a similar study carried out by Bejaoui and Guirat [33] in Tunisia reported that deferoxamine was the most commonly used iron chelator (57.3%), whereas oral chelators had been administered only to 29.1% of their patients [33].

Our result is not in agreement with a similar study from western India carried out by Shah *et al*. [42], who reported that out of 67% of their thalassemic patients who received chelation therapy, 98% were receiving oral chelation therapy and only 2% were taking desferrioxamine. Poor compliance with deferoxamine therapy is because of the difficulties associated with transfusion as it is injected subcutaneously and requires a long duration of infusion of 8 h. In addition, the noticeably increased percentage of patients receiving oral chelation therapy in India was because of the reduced cost of oral chelating drugs through manufacture of similar cheaper formulations locally in India [58,60,92]. In 2017, a study carried out in Bangladesh showed that the majority of their thalassemic patients used oral chelator therapy, whereas only 9.4% of the patients used intravenous Desferal [28].

The three chelating drugs have major differences in efficacy, tolerance, site of action, toxicity profile, and cost, all of which affect the morbidity and mortality of iron-overloaded patients in both developed and developing countries [92]. In most western and other developed countries, the selection of the chelating drug for the treatment of thalassemia depends on the choice of the physician, the commercial influence of pharmaceutical companies, and drug policies of the regulatory authorities [59,60].

Iron overload is the primary and major risk factor of mortality and morbidity in thalassemia major despite advances in chelation therapy [52,74,93,94]. The cut-off limit for serum ferritin is less than 1000 ng/ml between adequately chelated and poorly chelated patients [61,62]. The mean serum ferritin level among our studied cases was 2350±600 ng/ml. The serum ferritin level was between 1000 and 3000 ng/ml in nearly half (48.4%) of the studied cases, between 3000 and 6000 ng/ml in 22.6% of the cases, between 6000 and 9000 ng/ml in 17.7% of the cases, less than 1000 ng/ml in only 8.1% of the cases, and more than 9000 ng/ml in 3.2% of the cases. Our result was in agreement with Belhoul *et al*. [46] who reported that the mean serum ferritin among their pediatric thalassemic patients in Dubai was 2597.2± 1976.8 ng/ml. In addition, in 2013, a similar study carried out by Bejaoui and Guirat [33] in Tunisia reported that iron overload between 1001 and 2500 ng/ml was found in 39.6% of their studied thalassemic patients, whereas 26.9% had a ferritin level between more than 2500 and 5000 ng/ml and only 6.9% had a ferritin level greater than 5000 ng/ml. In contrast to our result, Shah *et al*. [42] reported more adequately chelated patients (6.3%) than ours with serum ferritin level less than 1000 ng/ml [42].

We found the highest mortality rate (63.6%) among those with serum ferritin levels between 6000 and 9000 ng/ml and represented 50% of the total dead cases studied. In comparison, the mortality rate was

21.4%, about 40% less among those with lower levels of serum ferritin between 3000 and 6000 ng/ml, which further decreased to half (10%) among those with lower serum ferritin levels between 1000 and 3000 ng/ml and to zero among those with the lowest serum ferritin level (<1000 ng/ml), with a highly statistically significant difference (P=0.004). The difference between the mortality rate of 63.6% among those with serum ferritin levels between 6000 and 9000 ng/ml (11 cases) and the mortality rate of 50% among those with serum ferritin levels more than 9000 ng/ml (two cases) is not statistically significant because of the huge difference in the number of cases in each. This indicates that high serum ferritin level is a risk factor for early death and at lower levels of serum ferritin, the mortality rate decreased accordingly.

Our results are in agreement with the results from previous studies showing that serum ferritin level (persistently above 2500 ng/ml) is associated with reduced survival in thalassemia [57]. Similarly, Borgna-Pignatti *et al.* [95] concluded that the lower levels of ferritin are predictive of a better prognosis in patients with thalassemia major. In addition, a study carried out in Saudi Arabia showed that the serum ferritin levels of patients who died were significantly higher than those of patients who survived (7500 vs. 3200; P<0.001) [56]. Another study carried out in Iran reported that the survival time showed a significant inverse relationship with the serum ferritin level (P=0.0087) [57]. A multicenter study in Italy also confirmed that high serum ferritin levels contribute toward the risk of death in patients with thalassemia [63].

Complications of blood transfusion and iron overload were detected in 41.3% of our studied cases. The most common complication of blood transfusion and iron overload among our studied cases was cardiac dysfunction in the form of cardiomyopathy, representing 19.3% of the total studied cases and around half of the complicated cases (46.7%), followed by liver disease (11%), nephropathy (6.4%), and infection (hepatitis) (3.7%). The high prevalence of complications in our population stresses the need for further evaluation and improvement in the management of thalassemic patients in Yemen. The reasons are probably multiple transfusions, lower pretransfusion hemoglobin level, and inadequate chelation therapy, and severe anemia, if not treated well, can result in high-output cardiac failure [96]. Our results are in agreement with Chern *et al.* [97], who indicated that among the living thalassemia patients older than 15 years of age, heart failure and arrhythmia are common complications. Similarly, in 2013, Bejaoui and Guirat [33] reported that 19.8% of their studied thalassemic patients in Tunisia had heart disease [33]. A study in Hong Kong found that cardiomyopathy was present in 15.1% of their patients [45]. In addition, around 15.1% prevalence of cardiac involvement was reported among Sicilian thalassemic patients [98].

In contrast, Borgna-Pignatti *et al.* [99] reported that the prevalence of complications in Italian thalassemic patients includes heart failure in only 7%. In 2013, Belhoul *et al.* [46] reported a much lower incidence rate of cardiomyopathy (1.8%) among their thalassemic patients studied in Dubai.

The mortality rate among our studied thalassemic patients was high (27.5%). Cardiac dysfunction was a major risk factor of death among our thalassemic patients. About 60% of the deaths were because of cardiac complications and the mortality rate was 85.7% among cases with cardiac complications with a high statistically significant difference (P=0.000). This could be explained by the facts mentioned in earlier reports that myocardial iron loading and heart failure contribute toward the high mortality of thalassemia major [33,100,101] and thalassemic patients treated with transfusion and adequate chelation have better survival and a lower frequency of heart failure and arrhythmia [95].

Our result is in agreement with Hajipour *et al.* [91] who showed that the mortality rate among thalassemic Iranian patients was 27.4%. Similarly, other studies reported that cardiac failure and rhythm disturbances remain the main causes of death among thalassemia major patients [102,103]. Our study is also consistent with Al-Nood [19] who reported that cardiac dysfunction constitutes the first important cause of death, followed by infection. In addition, a Lebanese study reported that heart failure was the leading cause of mortality in Lebanon, with 58% of patients succumbing to cardiac decompensation [39]. Similarly, an Italian study reported heart failure is the cause for 50% of the mortality among their studied thalassemic cases [63].

In comparison, a lower mortality rate of 13% was reported in a similar study carried out by Bejaoui and Guirat [33] in Tunisia with heart failure as the main cause of death (39%). In 2015, Zamani *et al.* [32] also reported that in the Hamdan province in Iran, out of their 133 studied thalassemic cases, 16 deaths occurred, resulting in a mortality rate of 12%. A noticeable further lower mortality rate (5.2%) was reported in Saudi Arabia among their thalassemic patients; 3.3% of them died from heart disease and 1.9% died from infection [56]. The relatively high mortality rate among

transfusion-dependent β-thalassemia major patients in Yemen could be explained by the fact that treatment of thalassemia is complex, expensive, requires a multidisciplinary approach, and poverty, because of which patients are unable to buy iron chelating agents that help in decreasing the prevalence of complications among patients.

Limitations

The limitation of our study was difficulty in contacting some patients' families who were not living in Sana'a; thus, we contacted them by telephone and some did not even have a telephone line where they lived. In addition, both the unstable situation of the country and the problems that the country has been facing such as lack of electricity and lack of oil and financial problems make it difficult for the patients to reach the centers of the Yemeni Society of Thalassemia and Genetic Blood Disorders. In addition, the low education status of some patients' families and the low awareness of the exact clinical situation of their children caused some difficulties while attempting to obtain information from them.

Conclusion

Thalassemia is one of the major public health problems in Yemen. The high complication and mortality rates in our country are because of several reasons: lack of knowledge of thalassemia and its genetic aspects, late detection of the disease, unavailability of some of the chelator agents because of the unstable current situation, low incomes of the concerned population, and the absence of a national insurance system, all of which lead to difficulties in follow-up of the patients, buying the costly chelating agents and affording proper treatment.

Prioritizing thalassemia awareness and access programs for the targeted population should be designed through innovative approaches. Public education about thalassemia should be provided through periodic meetings addressed to health professionals including doctors and nurses working in the community, and family members.

Providing free iron chelating therapy in a sufficient and regular manner for all patients is important. Money donation is important to decrease the financial and psychological load to the patient and their families.

The management of thalassemia is multifaceted and expensive. However, its prevention is cost effective. Preventive measures such as health education, carrier screening and PMS, genetic counseling, and prenatal diagnosis remain the best ways to decrease the incidence of the disease, which might be reflected in financial savings, and social and health benefits. Prevention of thalassemia is therefore likely to be the most viable strategy to reduce the burden of thalassemia patients on families and to manage a sustainable healthcare system.

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Conflicts of interest

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