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ORIGINAL ARTICLE

Analysis of Survival in Patients with β-thalassemia Major in Guilan, Northern Iran

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ABSTRACT

Background: Advances in treatment of thalassemia major (TM) have improved life expectancy and survival of the patients. This study was conducted to assess survival rate of these patients in Guilan province, Northern Iran.
Methods: In this cross-sectional study, records of 1243 patients with TM from 2001 to March 2016 were evaluated in Guilan province. Sources of data were health centers of the province and territories, blood transfusion organization, general hospitals and private clinics. Data were analyzed using Kaplan–Meier method.
Results: 958 (77%) patients were born before 1997, the year that screening program of β-thalassemia in Iran was started. No case of β-TM was born during the last 5 years of the study. The 5, 10, and 15-year survival rate for all patients were 100%, 100%, and 99.6%, respectively. Hepatitis C infection was associated with decreased survival rate.
Conclusion: Survival in patients with TM has dramatically improved over the recent years and future studies about causes of death in these patients are highly recommended.

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Introduction

Thalassemia syndromes, a common group of genetic diseases worldwide, are associated with mutations influencing synthesis of globin chains. There are two main types of thalassemia, alpha and beta, in terms of absent or decreased production of alpha and beta globin chains, respectively.[1] According to increasing severity of clinical and hematological findings, beta-thalassemia is classified as the beta-thalassemia trait, beta-thalassemia intermedia, and beta-thalassemia major (TM).[2] It has been reported that the prevalence of beta-thalassemia is mainly high in the Middle East, Mediterranean countries, Central Asia, India, Southern China, Africa, and in South America.[3] The incidence rate of carriers of hemoglobin disorders is around 5.2% of the world population and more than 300,000 infants with severe hemoglobinopathies are born annually.[4] Furthermore, it has been estimated that thalassemia led to 18000 deaths in 2010.[5]

TM is usually diagnosed between 6 to 24 months of age. TM is associated with severe and advanced anemia due to ineffective erythropoiesis, extension of bone marrow resulting from extramedullary hematopoiesis, iron overload as a result of frequent blood transfusions, hepatosplenomegaly, reduced growth, increased risk

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of viral hepatitis, iron deposition in endocrine system due to chronic transfusion with resultant complications such as diabetes mellitus, and hypothyroidism, bone abnormalities, hepatic cirrhosis, skeletal changes, gallstones, and vascular thrombosis.[3, 6] Patients without regular transfusion generally die earlier than age of 20-30 years. Patients receiving regular transfusion and proper iron-chelation usually survive beyond the fourth decade of life. Currently, cardiac complications such as heart failure and serious arrhythmias resulting from myocardial siderosis is the most common cause of mortality in patients with thalassemia.[3, 7]

Numerous studies have been performed regarding survival rate and potential factors influencing survival of patients with TM worldwide.[7, 8] In the last decade, significant improvement in survival and quality of life of patients with TM has occurred due to regular blood transfusions and novel iron chelating agents,[9] whereas still many infants with TM are born every year.[10] It seems that more effective approaches on prevention of complications or decreasing the mortality rate of the disease are still highly desired.

Iran as one of the Middle Eastern countries has a high prevalence rate of TM.[11] It has been estimated that around 300 infants with TM are born every year in Iran.[10] Also, the number of patients with TM in Iran is recorded to be more than 20,000.[12] Maximum prevalence of TM is reported from regions around the Persian Gulf and the Caspian Sea.[13] A thalassemia screening program was designed in 1997 by Iranian primary healthcare system for preventing genetic diseases that resulted in decreased birth rate of thalassemic children.[14]

Nevertheless, despite improvements of health care system, long-term survival of TM patients still continued to be poor in early 2000s.[11] Research in literature has shown studies from south and north of Iran on survival rate and associated factors in patients with TM; however, survival related factors were not completely understood.[11, 15, 16] So considerable participation is needed to find out the potential factors influencing long-term survival of patients with TM, especially in regions with high incidence of the disease.[16] Information concerning analysis of survival in patients with TM in Guilan province located in North of Iran is deficient. In this study, we aimed to determine the survival rate of TM patients in Guilan province.

Materials and Methods

This retrospective cross-sectional study was performed in 2016 in Guilan province. Patients with TM were qualified for inclusion in the study and patients with thalassemia intermedia were excluded. Data of the patients were extracted from records available in health care centers, blood transfusion organizations, general hospitals and private clinics from all over the province for a 15-year period from 2001 to March 2016. A questionnaire including gender, age, blood group, place of residence, education level of the parents, age at diagnosis, Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection as accompanied disease and age at death was prepared.

Analysis of survival rate and influence of the potential factors related to survival were performed using the Kaplan-Meier method. Analysis between groups was done by Chi-Square χ^2 test. $P<0.05$ was considered significant. Analysis was carried out using SPSS 18 statistical software.

This study was approved by research committee of Guilan Blood Transfusion Organization (Rasht, Iran; no 4061). All data available in the medical record of the patients was considered confidential.

Results

Medical records of 1243 patients with TM, with mean age of 26.9±8.7 years (5-65 years) was studied. Baseline characteristics are summarized in Table 1. There was not any report of new case of TM born during the last 5 years (Table 1). Only 6.6% of patients had parents with academic education. 40.7%, 32 %, 21.6% and 5.7% of the patients had blood group O, A, B and AB, respectively.

HBV infection was seen in 5 (0.4%) of the patients. There was no documented case of HIV infection. Analysis of HCV infection in patients showed a frequency of 19.6% and 2.3%, before and after year 1997, respectively which the difference was significant ($P<0.0001$).

Table 1: Baseline characteristics of patients with beta-thalassemia major in Guilan province

Variable	Number (%)
Age groups (yr)	
<5	0
5-14	91(7.3)
15-24	352(28.4)
25-34	599(48.3)
≥35	199(16)
Unknown	2(0.1)
Gender	
Male	606(48.8)
Female	635(51.2)
Unknown	2(0.1)
Place of Residence	
Urban	692(55.7)
Rural	539(43.3)
Unknown	12(1)
Date of birth	
Before 1997	958(77)
After 1997	285(23)
Hepatitis B	
Yes	5(0.4)
No	1117(90)
Unknown	121(9.7)
Hepatitis C	
Yes	174(14)
No	936(75.3)
Unknown	133(10.7)

Data are presented as number (%)

There was not any significant difference in the mortality rate of the patients based on the education level of the parents, the place of residence and their gender. However, there was significant difference in the mortality rate of the patients in terms of the HCV infection and date of birth (before or after 1997, Table 2).

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Table 2: Mortality rate of patients with beta-thalassemia major in terms of date of birth and hepatitis C infection.

		Alive (n, %)	Dead (n, %)
Date of birth	Before 1997	894 (94.3%)	55 (5.7%)
	After 1997	280 (98.2%)a	5 (1.8%)
Hepatitis C infection	Yes (n, %)	150 (87.2%)	22 (12.8%)
	No (n, %)	908 (97.2%)[b]	26 (2.8%)

[a]P=0.004; [b]P<0.0001

In the present study, the first death occurred at the age of 11 years. The 5-year, 10-year, and 15-year survival rate of patients with TM using Kaplan -Meier method were 100%, 100%, and 99.6%, respectively.

Discussion

The present study was undertaken to find out the probable association of some related factors with survival in patients with TM in Guilan province. The present study showed that 5-year, 10-year, and 15-year survival rate of patients with TM were 100%, 100%, and 99.6%, respectively. This finding indicated a dramatic improvement in survival of TM subjects over recent years.

In a recent study of 454 TM patients in Taiwan from 2007-2011,[17] survival rate was above %97. In several other studies performed in different countries such as UK,[18] Egypt,[9] Greek,[19] and Cyprus,[20] improved survival rate of TM patients was also shown. It was concluded that improvement in survival rate during recent years could be explained by several factors such as advance in iron chelation, accessibility to safe blood, access to non-invasive procedures in evaluation of tissue iron, early detection of complications, improved compliance of the patients and progress in other aspects of medical care and nutrition of the patients.[9, 17, 18, 21-23] However, survival rate of the patients with TM who live in countries with inadequate resources is still low.[21]

Rajaeefard and colleagues in a recent retrospective cohort study in southern Iran reported that 20-year survival rate of thalassemia patients was 85%.[16] In their study, 26.8% of the patients had thalassemia intermedia. In a study of 133 TM patients from Hamadan province (the West of Iran), survival rates of 10 and 20 years were 98.3% and 88.4%, respectively.[13] Hamadan province is among regions with low prevalence of TM. The present study showed better survival rate of TM patients as compared with the study conducted in 2007 in Zahedan (Southeast of Iran) where the 5, 10 and 20-year survival rate of the patients were 97.7%, 97% and 81.2%, respectively.[11] A study of 101 patients with TM referring to Bandar Abbas thalassemia center (southern Iran) from 1999 to 2005 showed that 68% and 50% of TM patients survived by the age of 20 and 30 years, respectively.[24] In their study, serum level of ferritin and molecular background of the patients were the main potential factors involved in survival rate.[24]

Survival rate of patients with TM in Guilan province seems to be higher as compared to other regions of Iran. Guilan province was among the first provinces at the beginning of thalassemia prevention program; people from this area were aware of the disease and showed excellent cooperation in the implementation of the program.

Analysis of survival time did not reveal any meaningful difference between two genders, likely due to the inheritance pattern of the disease.[11, 13, 25] This finding was in contrast to the study conducted by Borgna-Pignattiet al. and Telfer et al. in which female patients with TM had longer survival rates.[8, 26] Telfer et al. suggested that female patients were possibly more compliant with iron chelation therapy; however, data regarding serum ferritin levels was controversial,[16, 26] hence more research is needed on the subject of the association of gender with survival in TM.[8]

No significant difference in mortality rate was observed between urban and rural patients in our study. This finding is in contrast to a study conducted in Hamadan province in 2015, where survival rate was remarkably higher in urban patients in comparison to rural ones.[13] It could be attributed to similar accessibility to primary care facilities between urban and rural areas due to short distance between cities and villages in Guilan province.

Mortality rate was higher among patients with HCV infection. Chern et al. identified that infections were one of the main causes of mortality among patients with TM.[27] Roudbari et al. identified HCV infection as a risk factor for increased mortality in TM patients.[11] According to existing data, comorbidities are adversely associated with decreased survival rate in patients with TM.[13, 16] Although regular blood transfusion is essential for survival of patients with TM, it plays a major role in increased risk of transfusion transmitted infections.

The occurrence of HBV, HCV and HIV infection in TM patients in our study was 0.4%, 14% and 0%, respectively. HCV infection was observed in 2.3% of the patients born after 1997. Seroprevalence of HCV infection in 105 thalassemic patients from north of Iran, Rasht was reported to be high (above 55%).[28] A study of 200 multi-transfused patients with TM from India in 2010 showed that seroreactivity for HBV, HCV and HIV infections was 2%, 2% and 3%, respectively.[23] In a recent study, prevalence of HCV infection among 1113 TM patients from Guilan province during 2002-2012 was 13.6%.[29] Nevertheless, HCV infection was not reported in patients younger than 10 years old. It has been suggested that decrease in transfusion transmitted infections such as HBV, HCV and HIV among patients with TM might be due to several factors such as training of the blood donors, improving measures in donor selection and sample collection and increased yield of screening laboratory tests.[23]

Conclusion

The present study showed that the incidence rate of TM in recent years has been decreased so that no new case has been diagnosed with beta TM during the last 5

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years in Guilan province and less than 10 percent of the patients were in the age group of 5-14 years. In addition, more than 75% of the patients were born before 1997 which the thalassemia prevention program was not still implemented.

Overall survival rate of patients with TM has significantly improved over the recent years. Accompanied HCV infection was associated with lower survival rate. Prospective research regarding potential factors involved in survival of patients with TM is suggested.

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Conflict of Interest: None declared.

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