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.

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...
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.\textsuperscript{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.\textsuperscript{3, 7}

Numerous studies have been performed regarding
survival rate and potential factors influencing survival
of patients with TM worldwide.\textsuperscript{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,\textsuperscript{9} whereas
still many infants with TM are born every year.\textsuperscript{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.\textsuperscript{11, 12} It has been estimated that around
300 infants with TM are born every year in Iran.\textsuperscript{10} Also,
the number of patients with TM in Iran is recorded to
be more than 20,000.\textsuperscript{12} Maximum prevalence of TM is
reported from regions around the Persian Gulf and the
Caspian Sea.\textsuperscript{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.\textsuperscript{14}

Nevertheless, despite improvements of health care
system, long-term survival of TM patients still continued
to be poor in early 2000s.\textsuperscript{15} 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.\textsuperscript{31, 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.\textsuperscript{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 $\chi^2$ 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>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Age groups (yr)</td>
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<tr>
<td>&lt;5</td>
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</tr>
<tr>
<td>5-14</td>
<td>91 (7.3)</td>
</tr>
<tr>
<td>15-24</td>
<td>352 (28.4)</td>
</tr>
<tr>
<td>25-34</td>
<td>599 (48.3)</td>
</tr>
<tr>
<td>≥35</td>
<td>199 (16)</td>
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<tr>
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<td>2 (0.1)</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>606 (48.8)</td>
</tr>
<tr>
<td>Female</td>
<td>635 (51.2)</td>
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<tr>
<td>Unknown</td>
<td>2 (0.1)</td>
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<tr>
<td>Place of Residence</td>
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<tr>
<td>Urban</td>
<td>692 (55.7)</td>
</tr>
<tr>
<td>Rural</td>
<td>539 (43.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Date of birth</td>
<td></td>
</tr>
<tr>
<td>Before 1997</td>
<td>958 (77)</td>
</tr>
<tr>
<td>After 1997</td>
<td>285 (23)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
</tr>
<tr>
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</tr>
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<tr>
<td>Hepatitis C</td>
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<td>174 (14)</td>
</tr>
<tr>
<td>No</td>
<td>936 (75.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>133 (10.7)</td>
</tr>
</tbody>
</table>

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).
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, survival rate was above 99.7%. In several other studies performed in different countries such as the UK, Egypt, Greek, and Cyprus, 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. However, survival rate of the patients with TM who live in countries with inadequate resources is still low.

Rajaeefard and colleagues in a recent retrospective cohort study in southern Iran reported that 20-year survival rate of thalassemia patients was 85%. 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. 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. 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. In their study, serum level of ferritin and molecular background of the patients were the main potential factors involved in survival rate.

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

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

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.

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. Roudbari et al. identified HCV infection as a risk factor for increased mortality in TM patients. According to existing data, comorbidities are adversely associated with decreased survival rate in patients with TM. 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%). 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. In a recent study, prevalence of HCV infection among 1113 TM patients from Guilan province during 2002-2012 was 13.6%. 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.

### 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 years.
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.

Acknowledgement
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Conflict of Interest: None declared.

References
21. Amid A, Saliba AN, Taher AT, Klaassen RJ.


