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The survival analysis of beta thalassemia major patients in South East of Iran

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ABSTRACT

الأهداف: من أجل تحديد البقاء على قيد الحياة للمصابين بالثلاسيميا الكبرى BT في عملية نقل الدم والعوامل ذات الصلة في الجنوب الشرقي بإيران.

الطريقة: أجريت هذه الدراسة المقطعية في مدينة زهدان – إيران، في عام 2007م. اشتملت العينات على المرضى الذين تم تحويلهم من جميع المقاطعة إلى مركز زهدان للثلاسيميا، ما بين 1998م وحتى 2006م. تم جمع البيانات بالرجوع إلى ملفات المرضى التي تم تسجيلها بواسطة الموظفين أثناء عملية نقل الدم. شملت البيانات المعلومات الجغرافية والطبية، وفصيلة الدم RH، ونوع الدم المنقول KTB، وعدد عمليات النقل السنوية ANOT، والأمراض المحمولة AD، والهيموجلوبين Hb، ومستوى فيريتين. تم استخدام طريقة كابلين ــ ماير واختبار الرتب مع اختبار تراجع كوكس لتحليل البيانات.

النتائج: توفي 46 مريضاً من بين 578 مريضاً، و99% نجو في السنة الأولى. بلغت نسبة النجاة عند الأعمار: الخامسة – العاشرة – الخامسة عشر والعشرين عاماً 97.9% – 97% – 92.1% و81.2% على التوالي. كان لوقت البقاء على قيد الحياة علاقة ملحوظة مع عدد مرات نقل الدم السنوية ANOT (p=0.0053) ، ونوعية الدم المنقول KTB (p=0.003) ، والهيموجلوبين Hb (p=0.002) ، ومستوى فيريتين (p=0.0087)، والأمراض المحمولة AD (p=0.000).

خاتمة: إن استخدام عملية نقل الدم المنتظمة، والانتباه لفحص الدم المنقول يزيد من معرفة العوائل حول الأمراض لمنع احتمال الإصابة بالثلاسيميا في الجنين. أخيراً يعد اكتشاف ومعالجة الأمراض المحمولة ذو أهمية قصوا لإطالة فترة البقاء على قيد الحياة للمريض.

Objective: To determine the survival of beta-thalassemia major patients with transfusion, and its related factors in Southeast of Iran.

Methods: This cross-sectional study was performed in Zahedan, Iran, in 2007. The sample included patients who were referred from all over the Zahedan Thalassemia Center from 1998 to 2006. The data were collected using the patients' records, which were recorded by the staff during transfusion. The data included demographic and medical information (blood group, blood RH, the kind of transfused blood [KTB], annual number of transfusions [ANOT], accompanied diseases [AD], Hemoglobin [Hb] and ferritin level). For data analysis, the Kaplan-Meyer method, and Log Rank test together with Cox Regression were used.

Results: Forty-six of 578 patients died and 99% had survived for the first year. The ages survival proportions were 5 (97.9%), 10 (97%), 15 (92.1%), and 20 (81.2%) years. The survival time showed significant relationships with the ANOT (p=0.0053), KTB (p=0.003), Hb (p=0.002) and ferritin level (p=0.0087), and AD (p=0.000).

Discussion: Using regular transfusion, paying attention to screening of transfused blood, increasing the families' knowledge on the disease to prevent the bearing of thalassemia fetus, are recommended; finally, the detection and treating of the AD, are of great importance to extend the lifetime of the patients.

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Beta-thalassemia (BT) major is a severe hemolytic anemia, inheritable from parents who are carriers of BT minor. The anemia occurs in the early years of life and is usually accompanied by splenomegaly and bone changes.[1] The most common treatments of this disease include blood transfusion and bone marrow transplantation; though the latter is less attentive due to complications, inappropriate donors, high cost and possible failure. Iran is located on the thalassemia world belt with the highest prevalence of thalassemia over the world.[2,3] It is estimated that the rate of the thalassemia carriers in different provinces of Iran, is ranged between 1-10% with an average of 4.5%.[4] According to the formal statistics which are introduced by the Iranian health authorities, the number of beta thalassemia major patients are more than 20000.[5] In the province of Sistan & Baluchestan, Southeast of Iran, the number of beta thalassemia major patients was 51.9 per 100000 in 1998 that was increased to 59.4 per 100000 by 2001, which gives it the fourth place in the country.[5] According to the hereditary pattern of beta thalassemia minor and the social acceptability of inter-familial marriages, the marriage of carriers increases the prevalence of beta thalassemia minor to 50% of the population.[6] Therefore, in S&B province, the prevalence of beta thalassemia major (7%) is more than the average of the country which is 4%. It is even more than 7% in 2 towns of the province, Khash and Iranshahr.[7] The most important consequent of the disease is shortening of the patients' life. However, the patients' survival with may concern to some factors such as gender, ethnicity, and different level of the disease is unknown. In a study in Greece, the survival of these patients was 22.6 years.[7]

In another research in the North of Iran, 1010 thalassemic patients were divided into 2 groups according to their date of birth, before and after 1986. The survival rate of the 2 groups was 68% and 80% by the age of 30.[8] In a recent study in Canada it was proved that patients with the ferritin level of less than 2500 (gr/dl) have survived longer.[9] In another study in Taiwan, the researchers showed that the survival of the patients born after 1980 is better than others. Also, they demonstrated that patients under 15 years old had no complications.[10] A study in England showed that almost half of the patients had survived by the age of 35.[11] In the province of Hormozgan in South of Iran, it was found that 99% of the patients were alive until the age of 5, 93% were alive until the age of 10, 68% were alive until the age 20 and the survival age for half of them was 30 years.[12] It seems that preventing marriage between carriers in order to prevent the birth of beta thalassemia newborns is the best method to overcome the problem. Unfortunately, due to special economic, social, and cultural situations of the province, the prevention of BT newborn seems to be too difficult. The objective of the present study was to determine the survival of the patients with BT major, receiving blood transfusion in Sistan & Baluchestan province, Southeast of Iran and the factors involved with the survival time.

Methods. This cross-sectional study was performed in 2007 in Zahedan, Sistan & Baluchestan province, Southeast of Iran. The data were collected using the records of a number of 578 patients from all over the province referred to the Thalassemia Treatment Center, Zahedan, Iran during a period of 8 years from 1998 to 2006. It is the only center providing different services for the patients in the whole province. A number of 578 patients were diagnosed by the doctors and some of them died during the treatment. The inclusion criteria were regular visiting of those who were diagnosed as thalassemic patients and were referred to the center, and the patients who did not visit the center to receive their treatments for some time and there were no information on their current situation, or those who had applied for bone marrow transplantation, were excluded from the study. The center was formally established in 1998 and a file containing demographic and medical information (namely gender, age, ethnicity, the blood group, and RH, and the date of death for the dead cases) was opened and kept for each patient. The donated blood for transfusion is screened against a number of infections such as HIV, malaria, hepatitis. The frequency of transfusion depends on the hemoglobin (Hb) level; the lower Hb level, the more frequently transfusion. Normally, most patients receive almost one blood transfusion each month; therefore, all of them have to visit the center at lease once every month and the number of transfusions is recorded regularly. The levels of ferritin and Hb are measured every time upon their visit. If they are high, the patients receive necessary medicine from the doctors in the center. The kind of blood, washed or filtrated (with 2 different mechanisms in preparing for transfusion) was also recorded at the time of transfusion by the staff. The patients' accompanied diseases were another data recorded by the doctors at the time of the transfusion. The patients have regularly received transfusion since the center was established.

For data analysis, the Kaplan-Meyer method, and Log Rank test together with Cox Regression in Statistical Package for Social Science (SPSS version 15) was used to show the survival time and the effect of the most important factors involved with their survival. The $p<0.05$ was considered as the significance level. Also, the study was approved by the ethical committee of the Zahedan University of Medical Sciences.

Results. The patients included 333 (57.6%) males and 245 (42.4%) females, and the 46 dead cases included 30 males and 16 females. The patients' survival ranged between a minimum age of few months and maximum 43 years with a mean of 10.8, standard deviation 6.55 and the median of 10 years. Maximum survival was 43 years in male and 25 years in female. Regarding the ethnicity, the patients consisted of 211 Fars, 354 Balouch, and 13 Afghan. There were 2 kinds of transfusion, filtrated blood used in 568 patients (98.3%) and washed blood used in 10 patients (1.7%). Distribution of the blood groups A, B, O and AB in the patients was 22%, 32.9%, 39.1% and 6%, respectively. They contained 530 (91.7%) positive and 48 (8.3%) negative blood RH. A number of 147 patients (25.4%) showed to have the Hb level of ≤9 g/dl with 15 dead cases. The number of patients with Hb level of >9 g/dl, was 431 (74.6%) with 31 dead. The mean ± SD of the Hb level was 9.8 ± 2.7 with the median of 9.7 g/dl. The number of transfusion is usually 12 times in a year (monthly transfusion), but in patients with a low level of Hb, the number of transfusions was increased. One hundred patients (17.3%) had 12 transfusions in a year with 10 (21.7%) dead patients, and 478 patients (82.7%) had more than 12 times transfusion with 36 (78.7%) dead ones. The mean ± SD of the number of annual transfusions was 14.2 ± 2.82. Concerning the level of ferritin, 98 patients (18.6%) grouped as having the level of ≤1500 ng/ml, with 5 dead; 394 (75.0%) patients had the level of >1500 to 3500 with 29 dead, and 33 patients (6.0%) had the level of >3500 with 9 dead (there are some missing data on ferritin). The mean ± SD of ferritin was 2337.6 ± 924.75. A number of other diseases (accompanied diseases) such as heart disease, renal disease, Hepatitis B and C, and diabetes

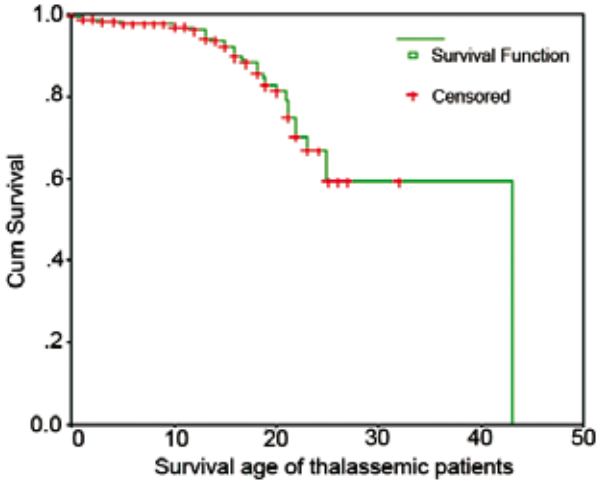

Figure 1 - The survival function of thalassemic patients at Zahedan, Iran in 2007.

Table 1 - The frequency of the total and dead patients together with the mean, SE and the result of Log Rank test on factors effective on survival in 578 Thalassemic patients in Zahedan, Iran (2007).

Variables	Frequency	No. of death	Mean ± SE of survival (Year)	Log rank test *P*-value
Number of annual transfusions				
1-12	100	10	19.5 ± 0.98	0.0053
>12	478	36	33.7 ± 1.87	
Kind of blood				
Filtrated	568	42	33.6 ± 1.84	0.003
Washed	10	4	17.7 ± 1.53	
Level of Hemoglobin *				
≤9	132	15	26.1 ± 1.56	0.002
>9	400	31	33.5 ± 2.04	
*Level of ferritin**				
≤1500	98	5	40.6 ± 1.36	0.0087
1500-3500	394	29	23.9 ± 0.54	
>3500	33	9	19.3 ± 1.12	
Accompanied diseases				
None	355	2	31.4 ± 0.46	0.000
Heart disease	126	27	26.0 ± 3.24	
Renal disease	5	4	13.0 ± 3.52	
Hepatitis B	6	0	No death	
Hepatitis C	39	4	23.9 ± 0.65	
Diabetes	17	4	22.05 ± 2.03	
Hepatitis and Diabetes	2	1	13.5 ± 2.47	
Liver disorder	28	4	17.0 ± 0.79	

*There are some missing values. SE - standard error

Table 2 - The result of Cox Regression model of the important factors effective on the survival of Thalassemic patients in Zahedan, Iran (2007).

Variables	B (SE)	*P*-value	Odds ratio Exp (B)	95% CI for Exp (B)
Level of Hemoglobin	-0.41 (0.17)	0.018	0.67	(0.47, 0.93)
Number of annual transfusions	-0.20 (0.055)	0.000	0.82	(0.74, 0.91)
Accompanied diseases				
Heart disease	3.12 (0.74)	0.000	22.65	(5.32, 96.49)
Renal disease	3.97 (0.91)	0.000	53.25	(8.9, 318.6)
Hepatitis C	1.84 (0.88)	0.036	6.29	(1.13, 35.02)
Diabetes	2.85 (0.89)	0.001	17.26	(3.03, 98.4)
Diabetes and Hepatitis	5.51 (1.28)	0.000	248.21	(20.37, 2023.74)
Liver disorder	3.61(0.88)	0.000	37.12	(6.67, 206.89)

B - coefficients of regression model, SE - standard errors of the coefficients
CI - confidence interval, Exp (B) = e^B

were observed in some of the patients, especially in the dead ones. For example, 27 (58.7%) of the dead patients had record of heart diseases in their files.

Figure 1 shows the survival function of thalassemic patients. At first year the survival of the patients was 98.9%. The age survival proportions of the patients were 5 (97.9%), 10 (97%), and 15 (92.1%) years. (**Figure 1**). Using Log Rank test, the survival time showed significant relationship with the number of annual transfusions, the kind of blood, the levels of Hb and ferritin, and the accompanied diseases.

Table 1 shows the factors with their means and SDs together with the p-value of Log Rank test. There was no significant difference of survival years between different genders, different ethnic groups, blood groups, and the positive and negative blood RH.

Table 2 shows the result of Cox regression where the survival time is the outcome variable, and the others are the predictors. **Table 2** shows that if the Hb level increases by one, the risk of death reduces approximately by 33% and if the number of transfusion increases by one, the risk of death reduces by 18%. Also, all accompanied diseases (except hepatitis B which had caused no death) increase the death hazard. This hazard was the highest in diabetes + hepatitis, and it was lowest in hepatitis C.

Discussion. It was found that the survival proportions of the thalassemic patients in Southeast of Iran until 5 and 10 years of life were 97.9% and 97%, respectively. This percentage was reduced to 81.2% by the ages of 20 and 59.3% by the ages of 25. This result is similar to a recent study in Hormozgan, at South of Iran.[12] In consistent with some other studies,[7,12] no significant difference of survival time was seen between 2 genders, probably because it is a hereditary anemia. However, there is a report of significant difference in survival time between 2 genders in another study.[13] Significant association was observed between the ferritin level and the survival time which is similar to a study in Canada.[9] Furthermore, the results showed that the level of ferritin is related to the disease and a low level of ferritin causes heart diseases in thalassemic patients as reported previously.[7,13] The present study showed no association between the patients' blood groups and the survival time. This is in agreement with another study that proved no relationship between blood groups and the thalassemia result (death-survival), and survival time.[12] The study also mentioned that the increased number of transfusions is an important factor involved with the survival time. The survival time increases with the increased number of transfusion. This was the same as the results of 2 other studies.[9,14] Although, transfusion is necessary for the patients' survival and this is the best method to suspend the complications of the disease, it can cause other problems for the patients such as infection transmission, namely Hepatitis B and C, HIV, malaria, toxoplasmosis, visceral leishmaniasis. Meanwhile, skeletal changes, the disorder of endocrine glands, cardiac symptoms, and complications, and renal disorders are examples of other disorders which might occur soon in these patients.[15]

There was a relationship between accompanied diseases and the survival time. The heart and renal diseases were the most causes of the death in the thalassemic patients. A study in Italy with 977 patients, showed that heart diseases were the cause of death in 67% of the thalassemic patients. Of these patients, 6.8% had heart failure and 7.5% had cardiac arrhythmia.[13] Similar to a recent study,[12] the survival time was significantly different between 2 kinds of transfused blood; the patients who received filtrated blood, survived longer than those who used washed blood. The results showed that the patients with a high level of Hb had a longer survival. Since frequent transfusion is necessary for these patients's survival, it is useful to teach the families of thalassemic patients to take them to the centers for regular transfusions. Also, it is necessary to screen the blood before transfusion in order to decrease the incidence of infections, especially diseases such as Hepatitis B and C. Even if the parents and the authorities do their best to reduce the problems of thalassemic patients, the survival time and life quality of the patients will remain low, in comparison with others. Also, the treatment cost of the thalassemia patients is very high and families with low income cannot pay the cost. Furthermore, the families in Sistan & Baluchestan province have less knowledge on the disease and the way of prevention. However, the disease is widespread, especially at the borders of the country. The best solution for the problem is to increase the knowledge of the people on the disease and the methods which can be used to prevent it. Also, the authorities are strongly recommended to pay more attention in arranging screening tests before people's marriages in order to find the carriers and prevent the extension of the disease. This mechanism can help to find the minor carriers of the disease and prevent the marriages which lead to the birth of thalassemic major newborns or provide them with necessary advices. Since regular recording of the patients' medical information is very important for patients' health and treatment, and this recording had not be carried out appropriately, it can be mentioned as one of the limitations of the study. For example in some cases the patients' deaths were not recorded regularly, especially in those who had died in other hospitals because of the complications of thalassemia.

In conclusion, the authorities of the center are recommended to record the patients' medical data and their mortality regularly. Also, the factors which can

increase the patients' survivals should be considered in their future treatment. Finally, further researches are required to find other factors involved with increasing of the patients' survival.

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