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Original Article

Contribution Factors on Long- term and Short- term Survival of Thalassemia Major Patients

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ABSTRACT

Introduction: Thalassemia major is an important health problem in Mediterranean countries that causes many psychological and economic problems. This study aimed to evaluate the effective factors on long- and short-term survival of thalassemia major patients using mixture and non-mixture cure survival models based on Generalized Gompertz distribution. The Generalized Gompertz distribution has flexible curve of failure rate that may be appropriate for different situation of survival analysis.

Methods: In this retrospective cohort study, medical records of 300 thalassemia major patients referring to Zafar's thalassemia clinic during 1994-2017 in Tehran, Iran were reviewed. Mixture and non-mixture cure survival models based on Gompertz and Generalized Gompertz distributions were performed to estimate the effective factors on long- term and short- term survival of Thalassemia Major Patients. The Akaike Information Criteria (AIC) was used to compare the models. Analysis was performed using SAS software version 9.4.

Results: The mean (±SD) survival time was 32.21 (±7.47) years. The censorship rate was 78.30%. In both of the mixture and non-mixture cure models, Generalized Gompertz distribution, as compared to the standard Gompertz had the lower Akaike criteria that was 200.8. Based on this model, iron deposition in liver at mild and moderate levels had a significant effect on the long-term survival of these patients.

Conclusion: Based on Akaike Information criteria, considering the Generalized Gompertz mixture cure model has the best fit for the data of thalassemia major disease in which patients are long-term survivors. In order to analyze the survival of patients with thalassemia major, since iron deposition in liver at mild and moderate levels had a significant effect on the long-term survival of these patients; it is recommended to apply a regular iron chelation therapy for extra iron excretion.

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Introduction

Thalassemia major is a chronic, progressive hemoglobin disorder requiring life-long blood transfusions. This disorder is highly prevalent among children in the Middle East, Mediterranean region, and South Asia.[1] However, only few studies on pediatric quality of life (PedsQL) have been published from Middle East, Mediterranean region, and South Asia.[2-4] Because the body lacks any effective way to remove excess iron, continuous blood transfusion can lead to iron overload which may result in hypogonadism, diabetes mellitus, hypothyroidism, hyperthyroidism and a lot of other health problems.[5, 6] In absence of an appropriate treatment, iron overload is the clinical consequence of chronic transfusions that can cause significant organ damage, morbidity, and mortality.[7] Nowadays the prognosis for thalassemia major has dramatically improved in the past two decades.[8]

In Iran, Khoei et al. (2015) reported the mean survival time of thalassemia major to be 29.1±0.47 years.[9] In Greece, Ladis et al. (2006) estimated the mean survival time of thalassemia major to be 22.6±6.2 years.[10] Various effective factors have been determined in the occurrence and severity of thalassemia major, including genetics, family history and patient's age at the time of diagnosis. In this regard, controlling of many other factors such as iron deposition or blood hemoglobin level could affect the longevity of these patients. Evidence suggests that early diagnosis and regular control of this disease could prolong the life of thalassemia major patients.[11] Management of the thalassemia major comprise regular blood transfusion and iron chelation therapy for extra iron excretion.[12-14]

With this background, it is very useful to further investigate this disease to reduce early death from thalassemia major.

Survival studies can deal with estimation of the survival distribution, comparisons of the survival distributions of different treatments or interventions, or explanation of the factors that affect survival times.[15]

The study of effective factors in the prevention, control and treatment of diseases is performed by statistical models for the approximation of the relevance between a set of covariates and the response variable, and the aim of fitting the model is to clarify and predict the response variable using covariates. Survival analysis is the study of survival times and the factors that affect them. Types of studies with survival outcomes include clinical trials, prospective and retrospective observational studies, and animal experiments.[16]

Some of the available models for survival analysis include non-parametric methods (Kaplan-Meier), semi-parametric analysis (Cox's proportional hazard model), and parametric models such as exponential, Gompertz, Weibull. Considering their flexibility and utility in function and performance, parametric models are of particular interest to many statisticians.[15]

In lifetime data analysis, the usual survival analysis techniques assume that all the subjects have the same chance to experience the events like disease and will finally experience that over an enough long time of follow-up. But the situation in which the studied population is a combination of uncured (susceptible individuals- who may experience the event of interest), and cured (non-susceptible individuals- who will never experience the event), the usual survival models may not be appropriate because they do not consider the probability of cure. A lot of patients with disease such as thalassemia

can have long-term survivors so cure models can be a useful tool to analyze and explain their survival data. Progress in the treatment of disease like cancer or thalassemia has led to develop cure models in statistical research. These models are useful in modeling lifetime data with long term survivors with a purpose to estimate the cure rate, survival distribution and the effect of covariates. Cure fraction provides useful information about the effects of various treatments and their differences in curable diseases.[17, 18]

In this retrospective observational study, the desired event is death. Also, we have right censoring because of cured individuals. Some important factors such as age at onset of deferoxamine-treatment, serum glutamic pyruvic transaminase, thyroid stimulating hormone, iron deposition in the liver, liver size, creatinine and hemoglobin that have been considered important factors in other researches were investigated in this study.

The mixture cure models were first introduced by Boag et al. (1949), to estimate the proportion of cure people for breast cancer in a set of data, which included 121 women (the event was the relapse of the disease).[19] Ladis et al. (2006) reported the significant effect of iron deposition in various organs of the body which was significant as the iron deposition in the liver in non-mixture cure model.[10] Age at onset of deferoxamine-treatment was important variable in Georgios et al. (2006) study, which studied the group comprised 45 asymptomatic transfusion-dependent patients with thalassemia major.[20] Mixture and non-mixture cure models are useful for determining the heterogeneity between cured and uncured patients; also, we can get information about censored and uncensored life time data. Totally when in a population, the mortality rate in the patients group return to the same level as general population, cure models are suitable for analyzing the data from these patients. Looking at the pattern of survival curve of patients in dataset is the easiest way to identify the presence of long-term survivors. If the survival curve has a plateau form at the end, then a cure model may be an appropriate choice for analyzing that dataset. We can get useful information about the covariates that associated with long-term and short-term survivors.[17] Edson et al. (2013) used mixture and non-mixture form of Generalized modified weibull cure models based on bayesian approach for gastric cancer data from 201 patients of different clinical stages. They note that when they compare the obtained deviance information criteria (DIC) values, both models (mixture and non-mixture) fit the data equally well .[18] Swain et al. (2016), used three parameters Gompertz distribution for estimating cure fraction, censored data and associated covariates for survival data of 284 patients with cancer under Bayesian approach, they used DIC for comparison between Weibull, Gompertz and Generalized Gompertz distribution and they conclude that Generalized Gompertz distribution has a better fit than the other distributions.[17] Martinez et al. (2017), fit cure fraction models based on Generalized Gompertz and modified Generalized Gompertz distributions under both of the Bayesian and maximum likelihood approaches. They concluded that the Bayesian estimates and Maximum Likelihood Estimates are almost interrelated, and both Bayesian and Maximum Likelihood approaches can be used to estimate the parameters of the modified Gompertz distribution. The DIC and AIC values related to the modified Generalized Gompertz distribution were less and had a better fit than the Generalized Gompertz distribution.[21]

In parametric survival models we assume the response variable, which is the survival time, follows a specific statistical distribution.[15] In analyzing lifetime data, the shape of hazard function is very important. For example, exponential distribution can have only constant hazard function whereas Gompertz distribution can have increasing and Generalized exponential distributions can have increasing or decreasing hazard functions. Weibull distribution has decreasing hazard function. In practice, for analyzing lifetime data we need a distribution that can have a bathtub curve shape hazard function.[22] In present study we used Generalized Gompertz distribution which has decreasing or unimodal probability density function and it can have increasing, decreasing and bathtub shape hazard function. Then the results were compared with the common Gompertz distribution. We provide the maximum likelihood estimates (MLEs) of the unknown parameters.

Materials and methods

This is a retrospective cohort study. Medical records of 300 thalassemia major patients referring to Zafar's thalassemia clinic during 1994 to 2017 in Tehran, Iran were reviewed in this study.

Survival function

Survival function is a basic quantity for describing the time necessary to occur in an optimal event for the phenomena concerned, which is the probability that each of the subjects studied will survive longer than the defined time t and is defined as follows:

$$S(t)= p(T>t) \quad (1)$$

This is a non-increasing and monotonic function that has a value of 1 in the begining and a zero value in infinity.
The survival function for the continuous random variable t with the probability density function f (t) is expressed as follows:

$$S(t) = p(T > t) = \int_t^{\infty} f(x)\, dx = 1 - \int_0^t f(x)dx = 1 - F(t) \quad (2)$$

Where F(t) is the cumulative distribution function of the random variable t.

Hazard function

Hazard function is another essential quantity in survival analysis. This function allows the instantaneous occurrence of the desired event in a unit of time, provided that survival is known to a specified time. In other words it is the failure rate at moment t.

$$h(t) = \lim_{\Delta t \to 0} \frac{p(t < T < t + \Delta t | T > t)}{\Delta t} \quad (3)$$

Mixture cure models

In this model, population is assumed to be divided to two heterogeneous sub-population, cured or long term survivors and uncured or susceptibles. Let p ($0 < p < 1$) be the probability of an individual being cured and (1-p) be the probability of an individual being susceptible.
The survival function in the mixture cure model for the entire population studied at time t is as follows:

$$S(t)=p+ (1 - p)\, S_0(t) \quad (4)$$

Where S_0 (t) is the baseline survival function for the susceptible individuals.

Non-mixture cure fraction model

A non mixture cure fraction model defines an asymptote for the cumulative hazard and hence for the cure fraction. In this case, the survival function is defined as:

$$S(t) = p^{F_0(t)} = exp[(\log p)]F_0(t), \quad (5)$$

$$F_0(t) = 1 - S_0(t) \quad (6)$$

Generalized Gompertz distribution

The survival and hazard function of this distribution are as follows respectively:

$$S_0(t) = 1-[1-\exp[-\frac{\lambda}{c}(e^{ct}-1)]]^{\theta},$$
$$F_0(t) = 1-S_0(t) \quad (7)$$

$$h(t) = \frac{\theta\,\lambda e^{ct}\exp[-\frac{\lambda}{c}(e^{ct}-1)]\,[1-\exp[-\frac{\lambda}{c}(e^{ct}-1)]]^{\theta-1}}{1-[1-\exp[-\frac{\lambda}{c}(e^{ct}-1)]]^{\theta}} \quad (8)$$

The Generalized Gompertz distribution covers some other distributions, for example common exponential distribution (Exp(λ)) with one parameter can be obtained by setting the parameter c to zero and placing the parameter θ equal to one.

Model comparison criteria

In the present study, we used the Akaike Information Criteria (AIC) to compare the mixture and non-mixture cure models based on Gompertz and Generalized Gompertz distributions. AIC is an approach to select the appropriate model by considering the number of the parameters and maximum likelihood function; accordingly, a better model has smaller AIC. This criterion can be calculated as follows:

$$AIC = 2K - 2\ln(L) \quad (9)$$

Where K is the number of parameters in the model and L is the maximum likelihood function.

In present study, univariate analysis was performed to investigate the statistical associations between dependent and independent variables. All variables with a P-value of less than 0.25 in the univariate analysis became candidates for entering the multivariate mixture and non-mixture cure models based on standard Gompertz and Generalized Gompertz distributions model.

To investigate the multicollinearity, multiple linear regression was used for the set of independent factors excluding the original response and one of the quantitative variables was considered as response and the multicollinearity checked. Then we used the variables with less multicollinearity as the independent factors for the original response.

After univariate analysis and checking multicollinearity of independent variables, some other variables were entered into the final model with the opinion of clinical specialist. Finally, the variables of location of birth, liver size, age at onset of deferoxamine, SGPT (Serum Glutamic Pyruvic Transaminase), blood creatinine level, TSH (Thyroid Stimulating Hormone), hemoglobin level, iron deposition in liver and location of birth were entered to multivariate mixture and non-mixture cure models based on standard Gompertz and Generalized Gompertz distributions to investigate their effect on long- term and short-term survival and select of the best model.

Mixture and non-mixture cure models

illustrated by NLMIXED SAS macro[22] were fitted to the thalassemia major patients dataset.

Results

All of the 300 available patient's data were evaluated in the fitted models. The mean (±SD) survival time for these patients was 32.21 (±7.47) years and the median (Interquartile Range (IQR)) survival time was approximately 33.00 (10.00) years. The minimum and maximum values for survival times were 12.00 and 53.00 years respectively. The frequency and percent for qualitative data, and mean and standard deviation for quantitative data are reported as tables 1 and 2.

Table 1. Distribution of Qualitative Characteristics of Patients with Thalassemia Major

Variable	Frequency	Percent
Liver size		
Normal	113	38.0%
Enlarged	184	62.0%
(S.G.P.T)		
Normal	201	67.2%
High	98	32.8%
T.S.H		
Normal	190	68.8%
Hypothyroidism	86	31.2%
Lt2ms		
Mild	88	29.4%
Moderate	57	19.1%
Severe	56	18.7%
Very severe	98	32.8%
Location of birth		
Next to the sea	87	29.0%
Away from sea	213	71.0%

Table 2. Distribution of Quantitative Characteristics of Patients with Thalassemia Major

Variable	Mean	Standard deviation
Creatinine	0.69	0.16
Hemoglobin	9.53	1.25

A total of 78.30% patients were found to be censored in this study by the means of existence of cured patients. The Kaplan-Meier estimate of the survival function is given in Figure 1, while the presence of a plateau near 0.70 confirms that cure model is suitable for this dataset.

As it is shown in figure 1, although beta thalassemia major patients have been studied for about 23 years, their survival rate does not reach zero and reaches a flat state near the 0.70. In addition, with considering the censorship rate 78.30%, it seems to be some evidence of existence of cured people in these patients.

Therefore, using cure models to analyze the survival of these patients seems reasonable.

According to the table 3, based on the Generalized Gompertz distribution in the mixture cure model, mild and moderate levels of iron deposition in the liver compared to very severe level, had a significant effect on the long-term survival time of patients with beta thalassemia major. From Table 3 and 4, it was observed that the results obtained for mixture and non-mixture cure models are different. Table 5 shows the AIC index obtained from the fit of different models.

As it is shown in Table 5, based on Akaike criteria Generalized Gompertz distribution in both mixture and non-mixture cure models had a better fit than the standard Gompertz distribution. The AIC index for Generalized Gompertz mixture and non-mixture cure models was 200.8 and 202.8 respectively, so mixture cure model fits the data better. According to the Generalized Gompertz mixture cure model that had the lowest AIC, iron deposition in liver at mild and moderate levels had a significant effect on long-term survival of these patients. According to Table 1, mild and moderate levels of iron deposition in liver had a significant effect on long-term survival of patients with

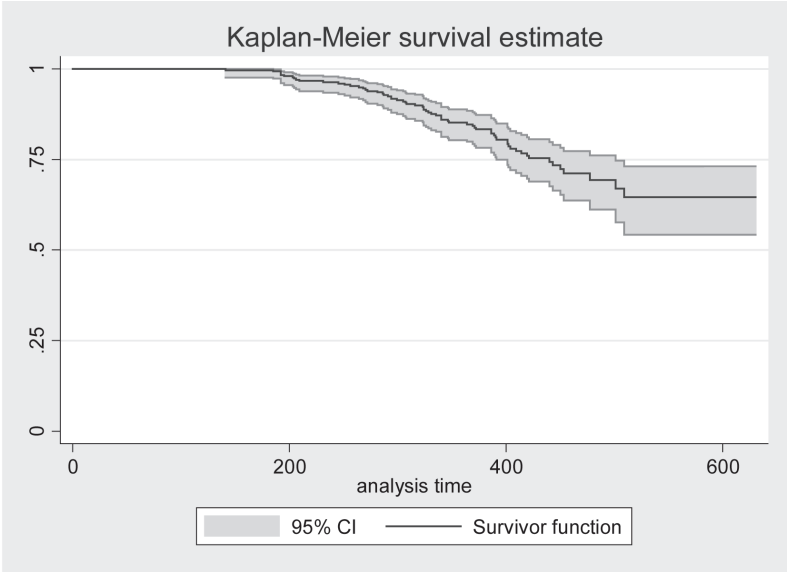

Figure 1.Kaplan–Meier survival curve

Table 3. Mixture cure model based on Generalized Gompertz distribution

Parameter	Estimate	SE	HR	CI	P-value
	Long time survivors				
Liver size			-		
Normal	-	-	0.938	-	-
Enlarged	-0.063	0.478	1.174	(-1.004,0.878)	0.895
Age for Onset of Deferoxamine-Treatment	0.161	0.103	-	(-0.042,0.364)	0.120
S.G.P.T			-		
Normal	-	-	0.395	-	-
High	-0.927	0.568	3.189	(-2.046,0.190)	0.103
Creatinine	1.160	1.717	-	(-2.219,4.540)	0.499
T.S.H			-		
Normal	-	-	0.677	-	-
Hypothyroidism	-0.390	0.471	1.377	(-1.317,0.537)	0.408
Hemoglobin	0.320	0.213	-	(-0.100,0.740)	0.134
Lt2ms			7.092		
Mild	1.959	0.608	6.252	(0.763,3.156)	0.001*
Moderate	1.833	0.695	1.083	(0.464,3.203)	0.008*
Severe	0.080	0.722	-	(-1.342,1.502)	0.911
Very severe	-	-	7.092	-	-
	Short time survivors				
Location of birth				-	
Next to the sea	-	-	-	(-0.786,0.093)	-
Away from sea	-0.346	0.223	0.707	-	0.122

SE, Standard Error; CI, Confidence Interval; HR, Hazard Ratio; S.G.P.T, Serum Glutamic Pyruvic Transaminase; T.S.H, Thyroid Stimulating Hormone; Lt2ms, iron deposition in the liver.
*Statistically significant

Table 4. Non-Mixture cure model based on Generalized Gompertz distribution

Parameter	Estimate	SE	HR	CI	P-value
Long time survivors					
Liver size					
Normal	-	-	-	-	-
Enlarged	-0.188	0.389	0.1000	(-0.955,0.577)	0.628
Age for Onset of Deferoxamine-Treatment	0.149	0.084	1.160	(-0.016,0.316)	0.078
S.G.P.T					
Normal	-	-	-	-	-
High	-0.602	0.433	0.547	(-1.456,0.250)	0.165
Creatinine	1.093	1.409	2.826	(-1.681,3.867)	0.438
T.S.H					
Normal	-	-	-	-	-
Hypothyroidism	-0.432	0.400	0.649	(-1.220,0.356)	0.281
Hemoglobin	0.203	0.176	1.225	(-0.126,0.533)	0.225
Lt2ms					
Mild	1.836	0.548	6.271	(0.757,2.916)	0.0009*
Moderate	1.513	0.583	4.540	(0.366,2.661)	0.009*
Severe	0.159	0.505	1.172	(-0.834, 1.154)	0.751
Very severe	-	-	-	-	-
Short time survivors					
Location of birth					
Next to the sea	-	-	-	-	-
Away from sea	-0.285	0.201	0.752	(-0.681,0.110)	0.156

SE, Standard Error; CI, Confidence Interval; HR, Hazard Ratio, S.G.P.T, Serum Glutamic Pyruvic Transaminase; T.S.H, Thyroid Stimulating Hormone; Lt2ms, iron deposition in the liver.
*Statistically significant

Table 5. Akaike Information Criteria for mixture and non-mixture cure models

Model	Standard Gompertz mixture cure	Standard Gompertz Non-mixture cure	Generalized Gompertz mixture cure	Generalized Gompertz non-mixture cure
AIC	215.5	221.9	200.8	202.8

beta thalassemia major. In this model, the coefficient of iron deposition at mild level is 1.959 and at medium level is 1.833, so the patients with lower amount of iron deposition in the liver, have longer survival time.

Discussion

This study aimed to show the flexibility and efficiency of the Generalized Gompertz model. Cure models based on this distribution had an appropriate fit for the data of thalassemia disease in which patients are long-term survivors. In present study iron deposition in liver at mild and moderate levels in both of the mixture and non-mixture cure models based on Generalized Gompertz distribution had a significant effect on the long-term survival of these patients.

If beta-thalassemia major is not diagnosed in the early months of birth, it can lead to death. So, in the early months of birth, the patients risk rate of death is very high. Onset of control

or treatment can significantly reduce the risk rate and with continued disease treatment and control, the risk rate can be fixed up to middle age. However, after middle age the risk rate increases as age increases. Therefore, the hazard function can be considered bathtub shaped.

Generalized Gompertz distribution due to the greater flexibility in the form of the risk function, covering all forms of the risk function and, the most importantly, the U-shaped hazard function, is appropriate in examining diseases such as the major beta-thalassemia function. Their risk is bathtub shaped. Ladis et al. (2006) reported the significant effect of iron deposition in various organs of the body which was significant as the iron deposition in the liver in present study.[10] This result is also consistent with the findings of Georgios et al. (2006), who assessed the effect of iron chelation therapy, claiming that poor compliance with chelation therapy was significantly associated with thalassemia major patients mortality.[20] Maggio et al. (2009), stated the significant effects of deferoxamine-treatment, as one of the risk factors for predicting mortality in patients with thalassemia major.[23] Moreover, in the study by Khoei et al. (2015), non-mixture cure model based on lognormal distribution was applied to determine the survival time of 296 thalassemia major patients, and age at onset of deferoxamine-treatment was observed to have a significant effect on short-term survival time, this result is consistent with the result of present study with mixture cure model.

By advancement of medical science, many diseases can be treated and controlled, so the use of cure models in clinical trials is increasing gradually because other survival models do not provide an estimate for proportion of cure patients. When we have a mixture of cure (who does not experience the event) and uncured individuals (who experience the event), cure models are very useful. In both of the mixture and non-mixture cure models long-term and short-term effects are considered. Cure fraction models are also reliable when cure patients are absent after an enough follow-up time and they will be reduced to standard survival models. Cure fraction models can be used based on many distributions with different hazard functions in lifetime data analysis. In this study we saw practically that cure models based on Generalized Gompertz distribution has a good flexibility in analyzing the data with long-term and short-term survivors for patients with thalassemia major. In survival analyzing, for enough long follow-up time when we saw a long and stable plateau at the tail of Kaplan-Meier survival cure we should realize that we may have a censored or cured individuals.

Conclusion

Mixture cure model based on Generalized Gompertz distribution had the best fit for the data and iron deposition variable in liver at mild and moderate levels had significant effect on long-term survival time with this model.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical Approval

This study was approved by the ethical committee of Iran University of medical Sciences (IR.IUMS.REC.1396.31987). In this study, no intervention was performed and the patients 'information was reviewed and kept confidential through the patients' files after

obtaining the consent of the patients and the relevant manager.

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