Health Science Monitor
2024; 3(1): 19-28
Published online (http://hsm.umsu.ac.ir)

Original Article

Factors affecting survival in bone marrow transplantation using mixture cure model

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Abstract

***Background & Aims*:** Bone marrow transplantation (BMT) is a curative treatment for various hematological malignancies. In standard survival models, the possibility of a cure has not been considered. Mixture cure models, which account for the possibility of a cure, can provide valuable insights into patient outcomes. The purpose of this study was to apply a smooth semi-nonparametric analysis for the mixture cure model to determine risk factors for survival and effective factors for the cure in bone marrow transplant patients.

***Materials & Methods*:** Data from BMT patients treated at Taleghani Hospital in Tehran were analyzed using a Weibull mixture cure model and an accelerated failure time mixture cure (AFTMC) model with an exponential kernel. The goodness-of-fit of each model was assessed using Akaike's information criterion (AIC).

***Results*:** The Weibull mixture cure model indicated that non-Hodgkin's lymphoma and acute leukemia were significantly associated with time to death. Age, recurrence after transplant, and hemoglobin levels were associated with the cure probability. The AFTMC model confirmed the prognostic effects of age, non-Hodgkin's lymphoma, and acute leukemia on time to death and further revealed that age and recurrence after transplant also influenced the cure probability.

***Conclusion*:** The smooth semi-nonparametric approach to mixture cure models provides a comprehensive analysis of BMT patient outcomes, identifying both prognostic and curative factors. This information can guide treatment decisions and improve patient survival.

***Keywords*:** Accelerated failure time model, Bone marrow transplant, Cure models, Semi-nonparametric density, Survival analysis

Received 26 June 2023; accepted for publication 06 November 2023

Introduction

Blood cancers are a group of cancers related to blood-forming tissues and are often characterized by a type of white blood cell that is affected by lymphoid or myeloid cells. The normal development of these abnormal cells is acute and chronic (1). The treatment of acute leukemia includes several steps, one of which is bone marrow transplantation (2). Bone marrow transplant is a process in which the patient's bone marrow is removed and replaced with healthy bone marrow (3). Therefore, the purpose of this transplant is to create healthy cells that can replace damaged cells inside the blood cells. Transplanted cells are capable of producing all blood factors, such as white blood cells, red blood cells, platelets, and other bone marrow stem cells (3). There are different types of bone marrow transplantation (4), which are selected according to the type of disease and the condition of the patient in order to bring well-being and recovery to the patient. The increasing use of this transplant has led to an increase in the number of children and adults who have lived longer despite suffering from malignant and nonmalignant blood diseases. Therefore, paying attention to the quality of life of these people has become increasingly important (5).

Over the past three decades, bone marrow transplantation has been widely used to treat patients with malignant or nonmalignant hematological diseases. One of the main goals of post-transplant follow-up is to predict the negative side effects of this treatment, including disease recurrence and transplant rejection, to determine preventive treatments (6).

An assumption in standard survival methods is that all people gradually experience a specified event such as death or recurrence (7). However, there may be situations in which some members of society are immune and do not experience the event, which are called cured or safe persons. In this case, standard methods do not work properly because they do not consider the possibility of recovery or improvement (8), and it is recommended to use cure models that have been developed to analyze time-to-failure data when a fraction of patients can be cured of the disease (9). One of the models that can be used in the data analysis of bone marrow transplant patients is the mixture-cure model (10).

Bone marrow transplant patients showed significant recovery after transplantation, and therefore, these patients can be analyzed in the form of cured models.

In mixture-cure models, it is assumed that the population is a combination of susceptible (non-cured) individuals who experience the event and non-susceptible (cured) individuals who will never experience the event (11). In general, in studies related to survival, if a percentage of people in the population are immune, cure models are used. Such as Kiwi et al.'s study (12). This study aimed to determine the risk factors and factors affecting the health of bone marrow transplant patients using cure models.

Materials & Methods

This study was a cohort study. The data consisted of bone marrow transplant patients who visited Taleghani Hospital in Tehran. Due to missing data and incomplete information, 340 patients with complete data were studied over a period of 9 years, from 2005 to 2016 (they were followed up for at least 5 years). The patients who were still alive at the end of the study were considered cured, and those who had no information after a certain time were considered right censored. In this study, the variable of transplant until death (survival time in months) was considered as a dependent variable and the variables of age, sex, type of transplant, disease diagnosis, hemoglobin, relapse after transplant, and relapse before transplant were considered as independent variables. This study was approved by the ethics committee of Tarbiat Modares University (ethics code IR. TMU. REC.1396.634).

The Akaike information criterion (AIC) was used to select the best model. The smaller the value of this criterion, the better the model (13). Two families of statistical distributions, Weibull and smooth semi-nonparametric (SNP), were used in the mixture cured models with the accelerated failure time (AFT) formulation for the survival part of the model (14). In SNP mixture cured models, the probability density function is approximated by a smooth family with a kernel of common distributions, such as exponential or normal. However, a more general and flexible density is obtained since it has a polynomial of the degree of k, to support more and flexible shapes.

Cured models are divided into two general categories: mixture and non-mixture (15). In this study, mixture cure models were used which is a combination of two types of patients. The first category was related to patients who were immune to death (cured), and the second category included patients who had no immunity (uncured) (16). It should be noted that in this study, the Kaplan-Meier survival chart was used to identify the overall cure rate of patients. That is, if the graph of the survival function before reaching zero comes to a plateaus level after the follow-up time, this is indicative of the presence of the cure rate (17). Data analysis and model fitting were performed using R software version 4.3.1 and the flexsecure package.

Results

Table 1 shows the descriptive results of the data, including the number of patients and their percentages for all the categories of variables. Of the 340 bone marrow transplant patients, 143 (42%) were female, and 197 (58%) were male. Of these patients, 118 (35%) had multiple myeloma, 41 (12%) had non-Hodgkin's lymphoma, 108 (32%) had Huntington's disease, and 73 (21%) had acute leukemia. The average age of the bone marrow transplant patients was 39 years, with a median age of 39 years and a standard deviation of 14.

Table 1. Patients' clinical, pathological, and biological characteristics.

Variable	Category	Number of patients (percentage)
Sex	Female Male	143 (42) 197 (58)
Age	Less than 35 35 years and older	143 (22) 197 (78)
Hemoglobin	grams per deciliter 10 > grams per deciliter 10 ≤	230 (68) 110 (32)
Diagnosis	Multiple myeloma non-Hodgkin's lymphoma Huntington Acute leukemia	118 (35) 41 (12) 108 (32) 73 (21)
Transplantation type	Allogeneic Autologous	75 (22) 265 (78)
Recurrence after transplantation	Yes No	284 (84) 56 (16)
Recurrence before transplantation	Yes No	226 (66) 114 (34)

The results of the multiple analyses by the Weibull parametric mixture cure model are shown in Table 2. The variables of non-Hodgkin's lymphoma and acute leukemia are factors affecting the time to death and thus, these variables reduce survival time. In addition, the analysis for the factors affecting the cure of patients also showed that the variables of age and recurrence after transplant reduce the chances of curing patients, and the variable of hemoglobin increases the chances of curing patients.

Table 2. The fitting results of Weibull mixture model in the presence of predictor variables.

Variable	Category	Cure		
		Estimate	Standard error	*p* value
Age	Less than 35†	-	-	-
	35 years and older	-1.342	0.540	0.012*
Hemoglobin	grams per deciliter 10 >†	-	-	-
	grams per deciliter 10 ≤	1.339	0.572	0.019*

Variable	Category	Cure		
		Estimate	Standard error	*p* value
Diagnosis	Multiple myeloma†	-	-	-
	non-Hodgkin's lymphoma	1.114	4.149	0.332
	Huntington	1.093	1.254	.383
	Acute leukemia	0.895	1.203	0.457
Recurrence after transplantation	No†	-	-	-
	Yes	-1.852	0.667	*0.005
Variable	**Category**	**Survival**		
		Estimate	**Standard error**	***p* value**
Diagnosis	Multiple myeloma†	-	-	-
	non-Hodgkin's lymphoma	-2.156	0.590	< 0.001*
	Huntington	-0.721	0.668	0.280
	Acute leukemia	-2.085	0.620	< 0.001*
Parameters				
Shape	-	-0.099	0.110	
Scale	-	4.771	0.428	
AIC	744.3			

†Reference category
*Significance at the 0.05 level

The results of the multiple analyses by the smooth semi-nonparametric AFTMC model showed that this model had a better fit for the data since it has smaller AIC. Table 3 shows the results of fitting the smooth semi-nonparametric model with an exponential kernel and $k = 1$. Based on this model, age and recurrence after transplantation are effective factors in the curing of bone marrow transplant patients. As the regression coefficients obtained in this case are negative for these variables, they have a decreasing effect on curing. That is, with an increase in these variables, the cure rate decreases. In addition, the investigation of factors affecting survival time also showed that the variables of age and non-Hodgkin's lymphoma and acute leukemia decreased the time to death, and the recurrence variable after transplantation increased the time to death.

Table 3. The fitting results of smooth semi-parametric analysis for the AFTMC model in the presence of predictor variable

Variable	Category	Cure		
		Estimate	Standard error	*p* value
Age	Less than 35†			
	35 years and older	-1.033	0.538	0.054*

Variable	Category	Cure		
		Estimate	**Standard error**	***p* value**
Hemoglobin	Grams per deciliter 10>†			
	Grams per deciliter 10≤	0.803	0.543	0.139
Diagnosis	Multiple myeloma†			
	non-Hodgkin's lymphoma	0.061	0.686	0.089
	Huntington	-0.159	0.729	0.827
	Acute leukemia	-0.468	0.704	0.506
Recurrence after transplantation	Yes			
	No	-3.282	1.458	0.024*
Variable	**Category**	**Survival**		
		Estimate	**Standard error**	***p* value**
Age	Less than 35†			
	35 years and older	-0.820	0.398	0.039*
Hemoglobin	Grams per deciliter 10>†			
	Grams per deciliter 10≤	0.340	0.471	0.470
Diagnosis	Multiple myeloma†			
	non-Hodgkin's lymphoma	-2.211	0.489	< 0.001*
	Huntington	-0.321	0.564	0.569
	Acute leukemia	-1.377	0.518	0.007*
Recurrence after transplantation	Yes			
	No	1.085	0.369	0.003*
Location		3.863	1.017	
Scale		0.980	0.168	
ϕ parameter		1.370	0.347	
AIC	739.930			

†Reference category
*Significant at the 0.05 level

Figure 1 shows the Kaplan-Meier curves, the fitted semi-nonparametric AFTMC model, and the estimated cure rate for bone marrow transplant patients. It is clear from the graph that the cure rate is approximately 62%.

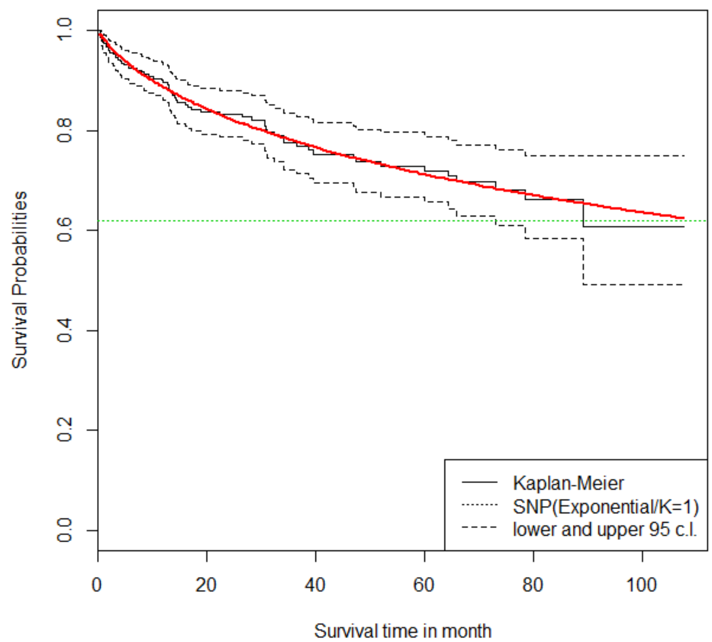

Fig. 1. Kaplan-Meier curves, the fitted semi-nonparametric AFTMC model with exponential kernel and $k = 1$ and the estimated cure ratio for bone marrow transplant patients.

Discussion

Bone marrow transplantation is a suitable treatment for many blood diseases including malignancies (18, 19). During the last two decades, bone marrow transplantation has been one of the main methods of choice for the treatment of some benign blood abnormalities, such as thalassemia, and malignancies, such as leukemia, lymphoma, and Hodgkin. In other words, the use of this treatment method has increased the survival rate of children and young adults who are affected by this type of disease (20).

One of the appropriate ways to monitor the progress of cancer treatment is to monitor the survival of patients over time (21). Survival analysis models that consider the cure rate are called cured models and play a significant role in the analysis of patient survival data (21). In common survival models, it is assumed that all individuals in a study are prone to the event and will eventually experience it. However, not all people may experience the event, and in this case, the use of conventional models will provide inaccurate estimates. The use of cured models while considering factors affecting survival and the cure rate solves this problem (22, 23).

The Weibull distribution is common in survival analysis, which is more flexible compared to the exponential distribution, and the assumption of proportional risk and accelerated failure time is established for it (7). Factors affecting the time to an event are among the most important outcomes of interest in clinical studies (24). Based on the Weibull parametric mixture cure model, non-Hodgkin's and acute leukemia are factors that affect the time to death (short-term survival). In addition, the examination of factors affecting the cure of patients showed that the variables of age, recurrence after transplantation, and hemoglobin level are effective for curing. The variables of age and recurrence after transplantation decreased the chance of cure, and hemoglobin increased the chance of cure. Therefore, disease diagnosis is a significant prognostic variable for predicting survival time and the occurrence of death in the process of bone marrow transplantation. In addition, age, recurrence after transplantation, and hemoglobin level affect the cure rate. Therefore, early diagnosis of the disease in the process of bone marrow transplantation and speeding up treatment can increase the cure rate. In the study by Saffar et al., factors such as age at the time of diagnosis, history of certain diseases, and blood factors were of great importance in predicting the death of patients (25). Smoking, marital status, and place of residence were other factors identified in the study by Saffar et al. In these studies, the effect of smoking has also been emphasized (25-28), which unfortunately could not be investigated in this study due to lack of patient information.

In a study by Khani et al. on multiple myeloma patients who were candidates for autologous bone marrow transplantation, it was shown that there was a significant difference in overall recurrence during the follow-up period (29). In this study, the effect of recurrence after transplantation on curing was significant in both models.

Since in this study, we examined the results of bone marrow transplantation in various blood diseases, we must also evaluate the factors involved before and after transplantation. These factors include 1-the type of disease, 2-condition of the disease, and 3-complications of the disease. In this study, due to the incompleteness of the recorded information, we were not able to fully and comprehensively examine the factors affecting the transplant process.

The most important concern after bone marrow transplantation is the possibility of disease recurrence. There is a 30-60% chance of disease recurrence, and the most important risk factor for recurrence is age (30). In the current study, according to the AFTMC model, age was one of the factors affecting survival time, and the risk of death was significantly different in such a way that with increasing age, the chance of cure decreased. In the study by Hajizadeh et al., autologous bone marrow transplant patients with age less than 30 years had a higher chance of being cured (10).

In another study using multifactorial analysis, it was found that age, disease status, and diagnosis factors are very important and affect the overall survival time (31). Autologous peripheral blood or bone marrow stem cell transplantation is a useful and effective treatment method for patients with non-Hodgkin lymphoma (relapsed or partial response to initial treatment) (32).

In this study, 340 patients (197 men and 143 women) underwent bone marrow transplantation (265 autologous and 75 allogeneic) and had a variety of malignant and non-malignant blood diseases, including multiple myeloma, non-Hodgkin's lymphoma, Huntington’s disease, and acute leukemia. Among the 118 patients with multiple myeloma disease who underwent transplantation, 93 did not relapse after transplantation, but 25 had relapsed. In addition, among 41 individuals with non-Hodgkin's lymphoma, 108 individuals with Huntington's disease, and 73 individuals with acute leukemia 35, 93, and 63 individuals, respectively, had no recurrence after transplantation, but, 6, 15, and 10 patients had a relapse, respectively.

In a study by Chaokai et al. on bone marrow transplantation in patients with acute lymphocytic leukemia, 46 and 44 patients underwent allogeneic transplantation and autologous transplantation, respectively. The results of this study showed that the survival probability of allogeneic transplantation was higher than that of autologous transplantation (33). In this study, we were unable to investigate this issue due to incomplete information.

In the SNP mixture cure model, the variables of sex, hemoglobin, type of disease, transplant type, and recurrence before transplantation were not significant, whereas, in the Weibull mixture cure model, hemoglobin was significant. That is, patients with a hemoglobin level greater than 10 deciliters have a better cure than patients with hemoglobin levels below this level. In the Weibull mixture cure model, variables such as sex, type of disease, type of transplantation, and recurrence before transplantation were not effective factors for patient curing; however, the variables of age and recurrence after transplantation were significant. Therapists and health officials should consider and pay attention to these factors. The results of the present study can be provided to research and treatment centers for more effective treatment of patients. It is also suggested that in future studies, other important variables such as smoking should also be recorded in patients' medical records.

Conclusion

The results of this research showed that cure models can be used as a suitable model for the survival analysis of bone marrow transplant patients. Therefore, the use of these models in the survival analysis of cure data is suggested.

Acknowledgments

None declared.

Conflict of interest

The authors have no conflict of interest in this study.

Funding/support

None declared.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Ethical statement

This research was conducted in accordance with ethical principles and received the ethics code IR. TMU. REC.1396.634 from the ethics committee of Tarbiat Modares University.

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