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Long-term Survival of Multiple Myeloma Patients using Cure Models

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Abstract

Introduction: Multiple myeloma (MM) is a kind of blood cancer that is caused by the malfunction of plasma cells and their uncontrolled growth, which leads to a decrease in the level of immunity and the formation of bone lesions, especially in the spine, skull, pelvis, and ribs. Common symptoms in MM patients include severe bone pain, kidney problems, anemia, and frequent infections. This study aims to employ appropriate cure models to estimate the cure fraction and prognostic factors affecting overall survival (OS) in MM patients who have undergone transplantation.

Materials and Methods: This study has analyzed the medical records of 52 patients with multiple myeloma who were admitted to Taleghani Hospital affiliated with Shahid Beheshti University of Medical Sciences in Tehran from January 2010 to August 2016 and were followed up until February 2022. Four cure models were applied to the data and it determined the cure fraction in the Inverse Gaussian model is higher than in other models, so prognostic factors affecting the survival of patients were examined using this model.

Results: The mean age at diagnosis was 53.07 (SD =6.4). The 5-year survival rate for MM patients was 74%, and the long-term survival rate for patients in this study was 54.7%. Using the Inverse Gaussian model, the cure fraction was estimated at 54.4%

Conclusion: This study applies cure models to find prognostic factors based on pre-transplant CBC test on the survival time of MM patients who have been treated with auto-HSCT, so the number of platelets pre-transplantation and the patient's age are effective predictors for overall survival.

Keywords: Cure Fraction, Inverse gaussian distribution, Multiple myeloma

1. Introduction

Multiple myeloma (MM) is a type of disorder in plasma cells caused by genetic mutations [1]. Multiple Myeloma is the second most prevalent type of blood cancer, accounting for 10% of all blood cancers, after non-Hodgkin's lymphoma [2]. About 1.8% of all new cancer cases and 2.1% of all cancer-related deaths are attributed to this particular type of cancer [3]. In 2020, there were 176,404 new cases of multiple myeloma worldwide resulting in 117,077 deaths. In Iran, 1092 new cases of multiple myeloma were reported, and 930 deaths were recorded [4]. Multiple myeloma has an incidence rate of 6.63 a mortality rate of 3.04 per 100,000 people, and the five-year survival rate of this disease is 58.3% [5]. MM is slightly more common in men than in women, and its prevalence in blacks is almost twice that of other races [6]. The typical age of patients at the moment of diagnosis is approximately 65 years [7]. According to the National Comprehensive Cancer Network (NCCN), multiple myeloma is classified into two subgroups, MGUS smoking myeloma (without symptoms) and multiple myeloma (with symptoms) [8]. Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition that often predisposes to multiple myeloma, which is

detected by the presence of abnormal proteins in the blood, so early detection and monitoring of MGUS can prevent the progression of multiple myeloma significantly prevented [9, 10].

One of the most important symptoms of multiple myeloma is bone sclerosis, which is often the first symptom that people notice, weakness in the arms and legs, fatigue, unexplained weight loss, and unexplained fever are other symptoms of this disease that over time These symptoms will increase [11]. Common complications of multiple myeloma can include hypercalcemia, kidney failure, infection, skeletal lesions, and anemia [12, 13].

Treatments for multiple myeloma depend on several factors such as genetic factors, the patient's age, general health, and stage of the disease, the treatment of MM includes immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, chemotherapy, and stem cell transplantation. [14].

One of the methods of treating multiple myeloma is chemotherapy, which is effective in improving clinical symptoms and increasing the survival time of patients, but it has side effects and it can be said that it is not a perfect treatment [15, 16]. In recent decades, autologous hematopoietic stem cell transplantation (auto-HSCT) has received much attention for the treatment of various types of leukemia [17].

The purpose of survival analysis is to model the survival time until the event of interest occurs [18]. In classic survival studies, it is often assumed that over time all the patients under study will experience death, but this assumption is not always valid in practice, so with advances in cancer treatment methods, a significant number of patients survive [19]. These people who have a longer survival time are known as the cure fraction or the fraction of long-term survivors. Cox or the log-rank test is not appropriate. It ignores the cure fraction because it leads to bias in the estimates [20]. In this paper, we are interested in modeling the cure fraction.

The most common modeling method of long-term survival studies is the use of the standard mixture model, assuming that the popular parent as $S(t) = p + (1 - p)S_0(t)$ by Berkson and Gage in 1952 has been presented [21].

Due to the importance of cure fraction models, various approaches have recently been proposed to estimate their values [22]. One of the ways to model the cure fraction is to use defective distributions [23].

Various studies have been conducted on the factors affecting the success of transplantation and the survival of MM patients, but due to individual differences and other factors related to patients, no general and comprehensive results have been obtained [24, 25]. Identifying effective prognostic factors is crucial for the treatment of multiple myeloma [16]. The purpose of this study is to calculate the cure fraction from the time of diagnosis to the death of MM patients to determine the overall survival of patients using cure models and compare these models to achieve greater accuracy. Also, the analysis of prognostic factors effective in the success of transplantation of patients with multiple myeloma, using the appropriate cure model, is of interest.

2. Materials and Methods

Patient

This study included 72 patients with multiple myeloma (MM) whose disease was diagnosed through blood tests and biopsies. All these patients underwent autologous hematopoietic stem cell transplantation following bortezomib-based induction at Taleghani Hospital affiliated with Shahid Beheshti Medical Sciences. Patient information, including prognostic factors and treatment history, was collected from archived medical records, and their latest condition was followed up using telephone calls. Some patients were excluded from the study due to the incompleteness of their files, so among the reviewed files, the information of 52 patients was analyzed for this study. Patients were diagnosed from January 2010 to August 2016 and followed up until February 2022. Overall survival (OS) was defined as the time interval between diagnosis and death from MM. Prognostic factors affecting the overall survival of patients were determined through CBC test. The patients who were alive at the end of the examination or when no information about their survival status was available at the time of follow-up were considered as right censored. According to the first test, prognostic factors including age of patients at the time of diagnosis, number of platelets (Plt), white blood cells (WBC), and hemoglobin level (Hb) were considered.

Statistical analysis

Using Inverse Gaussian, Kumaraswamy Inverse Gaussian, Gompertz, and Kumaraswamy Gompertz distributions, we analyzed the effect of age, hemoglobin (HB) deficiency, white blood cells (WBC) deficiency, and platelet deficiency, on overall survival time. Survival function for Inverse Gaussian [26, 27], Gompertz [28], Kumaraswamy Inverse Gaussian [23, 29, 30], and Kumaraswamy Gompertz [31] distributions are defined in (Formol 1-4).

Inverse Gaussian survival function (1)

$$S(t) = 1 - [\,\Phi\left(\frac{-1+at}{\sqrt{bt}}\right) + exp\left\{\frac{2a}{b}\right\}\Phi\left(\frac{-1-at}{\sqrt{bt}}\right)\,]$$

Gompertz survival function (2)

$$s(t) = P(T > t) = e^{-\frac{b}{a}(e^{at}-1)}$$

Where β indicates coefficients vector and x is the covariates vector, so for t>0, b>0, u>0, a<0

Kumaraswamy Inverse Gaussian survival function (3)

$$S(t|x) = \left(1 - \left[\phi\left(\frac{-1+at}{\sqrt{bt}}\right) + e^{\frac{2a}{b}}\phi\left(\frac{-1-at}{\sqrt{bt}}\right)\right]^{r}\right)^{u\,exp(\beta' x)}$$

Kumaraswamy Gompertz survival function (4)

$$s^{*}(t|x) = \left\{1 - \left\{1 - \left(\, e^{\frac{b-be^{at}}{a}}\,\right)\right\}^{r}\right\}^{u\exp(\beta' x)}$$

The parameters were estimated using the maximum likelihood method, and to determine the best fit, the model with the lowest AIC and BIC criteria was selected as the best-fitted model.

We fitted these models to the MM patient data. Analyses were performed in the R software, version 4.0.3 [32].

3. Results

52 patients including 26 men (50%) and 26 women (50%) diagnosed with MM who received BMT were studied; the mean diagnosis age was 53.07 with a standard deviation of 6.4 years and the median age was 53 years. Platelet (Plt) count lower than 150,000 U/µL is defined as thrombocytopenia. white blood cells (WBC) lower than 4000 U/µL are regarded as leukopenia, and A hemoglobin (Hb) level below 12 g/dL for women and lower than 13 g/dL for men is considered as anemia. The time between diagnosis and death due to MM is considered as overall survival (OS). Patients' characteristics are provided in Table 1.

The cohort lasted 12 years. The mean OS was 106.93[CI:91.4-122.4] months. The 5-year survival rates are estimated at 72.1%. After 87 months (Almost 7 years), the survival curve was shaped flat, and the estimated cure fraction was 57.2% [CI: 41.5, 78.7] (P-value < 0.001). Figure 1).

Table 1 . Patient characteristics

Variable	Men	Women	Total
Age	53.98±7.78	52.13±4.6	53.07 ±6.4
Overall Survival (Month)	103 ±10.9	105 ±9.9	106.9±7.8
Leukopenia	3 (5.7)	4 (7.6)	7 (13.5)
Thrombocytopenia	5(9.6)	4 (7.6)	9 (17.3)
Anemia	21 (40.3)	16 (30.7)	37 (71.2)
Total	26(50)	26(50)	52

Frequency (%) / mean ± SD

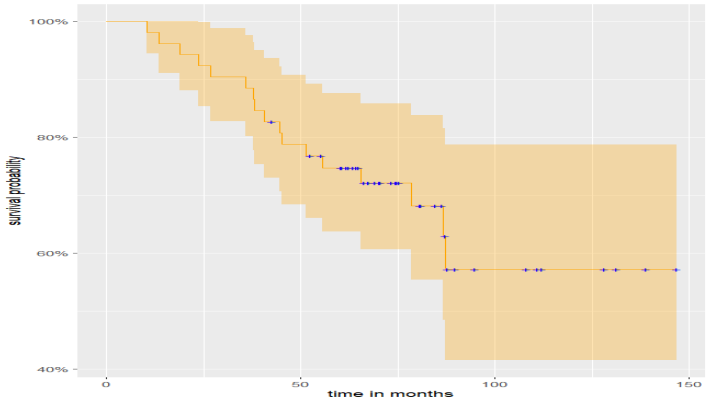

Figure 1: Kaplan-meier of os

Table 2 reports the maximum likelihood estimates of MM patients using the proposed regression models. The AIC and BIC criteria in the Inverse Gaussian distribution were 48.6 and 36.7, respectively; compared to other distributions, the Inverse Gaussian distribution has a smaller amount, which is considered an advantage. The cure fraction in the inverse Gaussian distribution was estimated as 54.7%, which closely aligns with the value calculated in the Kaplan-Meier curve, so the Inverse Gaussian distribution shows a better fit. This result was also confirmed in the study of melanoma patients by Rocha et al [31]. The fitted survival curves are presented in Figure 2.

We fitted the Inverse Gaussian model to the data, and the results of the univariate analysis using the Inverse Gaussian model are shown in Table 3, which shows that age at diagnosis has a significant relationship with the survival time of the patients; this confirms the results of the previous studies [14, 33]. Also, the number of platelets is effective in the survival time of patients.

Table 2. Maximum likelihood estimates for the fitted distributions for the MM data set

Model	$\hat{a}$	$\hat{b}$	$\hat{r}$	$\hat{u}$	$\hat{p}$	AIC	BIC
Inverse Gaussian	-3.61	0.535	1	1	0.547	48.67	36.77
Kumaraswamy Inverse Gaussian	-0.936	4.9	3.01	2.31	0.542	52.82	36.92
Gompertz	-5.93	-0.42	1	1	0.52	50.53	56.43
Kumaraswamy Gompertz	-0.15	1.78	0.68	-1.53	0.37	52.46	52.5

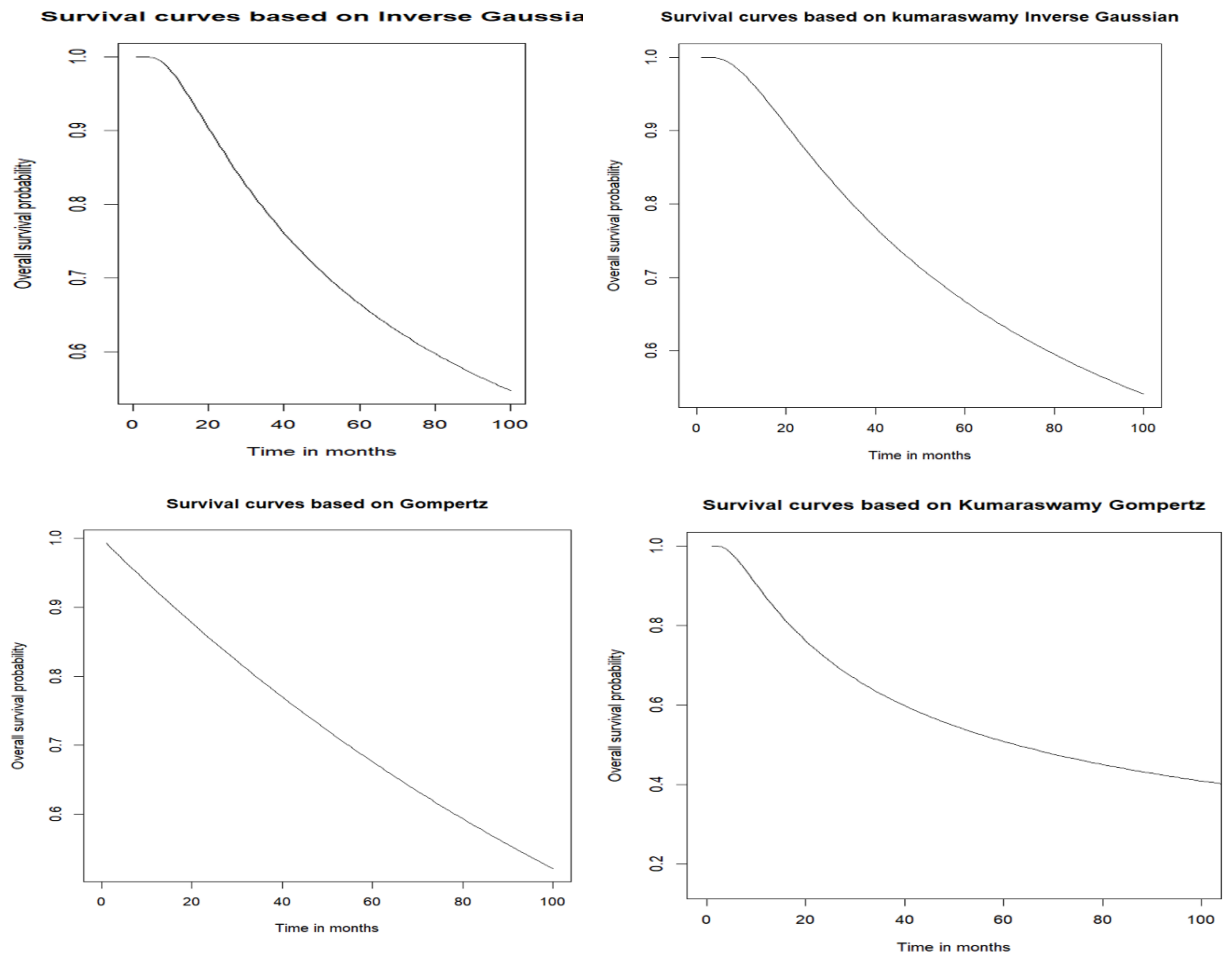

Figure 2 : The Fitted Models

Table 3. The results of univariate analysis

Variable	Inverse Gaussian		
	AIC	BIC	p-value
Age at diagnosis	42.97	47.88	0.00*
Hemoglobin (HB)	44.9	49.81	0.34
White Blood Cells (WBC)	45.78	50.69	0.93
Platelet (Plt)	42.78	47.69	0.009*
Sex	73.66	58.99	0.56
p-value<0.05			

Women had a slightly higher survival rate than men, but this difference is not significant, and in general, it can be said that gender does not have a significant effect on overall survival and recovery. This finding contrasts with previous studies that suggested a significant impact of gender [34].

4. Discussion

This study emphasizes the importance of using appropriate survival models to achieve more accurate results with less bias, one of the ways to achieve this is to use cure models [35]. Cure models are a popular topic in the statistical literature, but not widely recognized in the clinical literature [36]. With the progress of cancer treatment, many cancer patients can survive their disease in the long term; in such cases, cure models are considered as a suitable tool to estimate the proportion of cancer survivors. Several studies used cure models to estimate the proportion of multiple myeloma survivors [36,37]. In this study, we also used defective cure models to estimate the cure fraction, so that the Inverse Gaussian distribution estimated the cure fraction at 54.7%, a value closely aligned with observed outcomes. The cure models used in this study perform better than standard mixture models because they examine the effect of independent variables over time. For more information, please refer to Rocha et al [31,37]. The aim of this study is to investigate the prognostic factors effective in transplant success in patients with multiple myeloma. We used the cure models due to their accuracy and efficiency to estimate the cure fraction and compared them. Also, cure models were used to describe survival trends in multiple myeloma. According to the pre-transplant CBC test, we investigated the effect of prognostic factors on the success of the transplant.

According to previous studies, a low platelet level in the pre-transplant CBC test has been shown to be a risk factor for allogeneic hematopoietic stem cell transplantation [38]. In the present study, there is a significant effect between the number of platelets before transplantation and survival time (p=0.009). Therefore, it can be said that the lack of platelets in the CBC test pre-transplantation reduces the patient's chance of survival. Patient age is known as an important factor in transplant success; in many articles age over 65 years is introduced as a risk factor in transplant success of MM patients. In the present study, age had a significant relationship with the survival time of patients (p=0.000), which confirms the results of previous studies [14,39,40].

We did not find statistical evidence for the importance of gender on overall survival, while in some past articles, gender has been introduced as a factor influencing overall survival and treatment time. Thus, this disease is more common in men than women [41].

In this study, we analyzed multiple myeloma data using cure models. Cure models provide additional information beyond the standard Cox model analysis. Cure models show that increased survival is due to the greater number of patients who are treated (long-term survivors). Although the application of this article is focused on multiple myeloma, the investigated cure models can be useful for a wide range of cancers such as Hodgkin's disease, colon cancer, melanoma, etc. [36,37].

To achieve more accurate results, this study can be conducted with a larger sample size; in addition, patient information can be collected from treatment centers related to multiple myeloma patients from different regions.

5. Conclusion

In this study, the application of cure models was investigated using the defective cure distribution on patients with multiple myeloma and the proportion of survivors (cure fraction) was estimated. Because of their accuracy and efficiency, cure models were used to estimate the cure fraction and these models were compared. Compared to other cure models, the Inverse Gaussian model provides a more accurate estimate of the proportion of survivors and generally provides better estimates on the data of this study. According to

the results obtained by using the inverse Gaussian distribution, it was found that in the CBC test pre-transplantation, the number of platelets and the age of the patient at the time of diagnosis are factors affecting the overall survival (OS) of the patients.

Most of recent studies on the treatment of multiple myeloma pointed out the importance of studying the long-term survival of these patients. Therefore, the estimation of the proportion of survivors (cure fraction) and identification of effective factors helps researchers and doctors in the treatment of multiple myeloma.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted following the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.487) and informed consent was obtained from all the patients.

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Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

There were no conflicts of interest in this study.

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