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Long-term Survival of Multiple Myeloma Based on CBC Test at Diagnosis Using Defective Marshall-Olkin Cure Model

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Abstract

Introduction: As a malignant proliferative disorder, multiple myeloma (MM) is classified as a cancer of the immune system. Generally, a complete blood count (CBC) is the first test for a patient with symptoms of MM. Through CBC, physicians can monitor abnormalities in the blood. To normalize malignancies in their blood, patients must first go through conventional chemotherapy. Afterward, if eligible, subjects would receive high-dose therapy and hematopoietic stem cell transplantation (HSCT). Primarily, patients would be subjected to autologous hematopoietic stem cell transplantation (auto-HSCT).

Materials and Methods: This retrospective cohort study consisted of 56 MM patients who were diagnosed between January 2010 and August 2016 and were followed up until February 2022. The survival rate of MM patients was assessed based on CBC test at the time of diagnosis. The clinical conditions, i.e., Thrombocytopenia, Leukopenia, and Anemia, were extracted from the CBC test and were used as the desired prognostic factors in companion with age at diagnosis. Overall survival based on the mentioned factors was analyzed using the defective Marshall-Olkin gompertz cure model, which was programmed in R software version 4.0.3.

Results: The mean age at diagnosis was 52.76 (SD = 7.1). The probability of long-term survival for patients in this study was 46%, with five-year overall survival equaling 73.2%. Patients with thrombocytopenia had about 86% lower odds of long-term survival compared with patients with normal Platelet levels (Plt).

Conclusion: The present study indicates that deficiency in Plt count is a significant factor leading to poor survival of MM patients.

Keywords: Multiple myeloma, Long-term survival, Thrombocytopenia, Defective distributions

1. Introduction

There is no doubt that cancer is a leading cause of death and that it is a major obstacle to increasing life expectancy around the globe. The number of cancer cases in the world currently stands at 19,300,000; by 2040, it is projected to be 28,400,000, with an increase of 47%. Several factors contribute to this prediction

including aging and population growth. As a result, changes in distribution and population growth could exacerbate the problem [1].

As a malignant proliferative disorder, multiple myeloma (MM) is characterized by rapid cell proliferation. Mutations in plasmocytes can lead to MM due to a variety of factors [2]. When symptoms appear, physicians first prescribe a complete blood

count (CBC) to determine whether blood components are standard. It is widely acknowledged that conventional chemotherapy can improve patients' clinical symptoms and survival rates. However, conventional chemotherapy cannot cure multiple myeloma completely as with other hematopoietic malignancies [3]. Since the 1980s, autologous hematopoietic stem cell transplantation (auto-HSCT) has become widely available for treating many hematopoietic diseases including lymphoma, leukemia, and myeloma [4]. In spite of its high recurrence rate, auto-HSCT is significantly safer and more efficient than other treatments available for MM [5]. The prognostic factors for poor outcomes with HSCT treatment for multiple myeloma have been identified by researchers and may be modified in the future [6–9]. In this retrospective study, we analyzed the primary prognostic factors of patients with multiple myeloma who underwent auto-HSCT.

2. Materials and Methods

Patients

The study involved 56 patients diagnosed with multiple myeloma. All of these patients underwent auto-HSCT following a bortezomib-based induction at Taleghani hospital, which is affiliated with Shahid Beheshti University of Medical Sciences. Patient information, including prognosis and treatment history, was collected from archived medical records, and their last status was checked using phone calls. Subjects were diagnosed from January 2010 to August 2016 and were followed up until February 2022. We investigated the CBC test at diagnosis as a prognostic factor to overall survival (OS) of patients, defined as the timespan between diagnosis and death due to MM. Platelet (Plt) count lower than 150,000 U/ μ L is defined as thrombocytopenia, white blood cells (WBC) lower than 4000 U/ μ L 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. These clinical conditions were identified based on the first CBC test.

Statistical analysis

With the OS as the endpoint of interest, we analyzed the effect of age and deficiencies in Plt, WBC, and Hb using the defective Marshall-Olkin extended weibull (MO-ew) cure model [10]. Survival function for MO-ew family of distributions is defined as:

$$S(t|x) = \frac{\exp\{\beta'x\} \exp\{-vH(t,\gamma)\}}{(1 + \exp\{\beta'x\}) \exp\{-vH(t,\gamma)\} - 1}$$

Where β indicates coefficients vector and x is the covariates vector. The function $H(t,\gamma)$ varies among

members of the family with every member having their unique parameter vector γ . v is the common parameter in the family. Parameter estimation was performed using maximum likelihood method and the best performance among this family was chosen in terms of lower AIC and BIC. The cure rate for MOeW model is computed based on the following formula:

$$p = \lim_{t \rightarrow \infty} S(t|x) = \frac{\exp\{\beta'x\}}{1 + \exp\{\beta'x\}}$$

As some of the event times were not specified exactly and given by an interval of time by respondents, we utilized the MO-ew model under interval-censored survival times. All the important prognostic factors were selected using the backward elimination procedure [11]. Statistical analysis was programmed using R software, version 4.0.3 [12].

3. Results

The cohort lasted 12 years. The median OS was 9.78 years, with a 5-year OS equaling 73.2% [95% CI: 61.7, 87.0]. The mean age at diagnosis for patients in this study was 52.7 years [95% CI: 38.9, 66.6]. Patients' characteristics are provided in Table 1.

After 10 years, the survival curve was shaped flat, and the estimated cure rate was 46% (P-value < 0.001) using the MO-ew gompertz model (Figure 1). Results from single and multiple analyses are summarized in

Table 1. Patient characteristics

Variables	Frequency (%) / mean $\pm$ sd
Age	52.76 $\pm$ 7.1
Status	
Died of myeloma (exact date)	8 (14.3)
Died of myeloma (interval censored)	11 (19.6)
Right censored	37 (66.1)
Gender	
Male	29 (51.8)
Female	27 (48.2)
Thrombocytopenia	
Yes	9 (16.1)
No	47 (83.9)
Leukopenia	
Ye	17 (30.4)
No	39 (69.6)
Anemia	
Yes	31 (55.4)
No	25 (44.6)

Table 2. We first did a single variable analysis and, finally, the ultimate model involved thrombocytopenia

as the only predictor. At the time of diagnosis, patients with normal Plt counts had 7.5 times more odds of surviving length than thrombocytopenic patients ($p =$

0.005). The estimated cure rates were 13% (P-value = 0.98) for thrombocytopenic patients and 52% (P-value < 0.001) for the others (Figure 2).

Table 2. Results

Variables	Estimations of MO-ew gompertz model					
	OR	Single 95% CI	Sig.	OR	Multiple 95% CI	Sig.
Thrombocytopenia						
No	7.50	(1.80, 30.48)	0.005*	7.50	(1.80, 30.48)	0.005*
Yes	-	-	-	-	-	-
Leukopenia						
No	0.82	(0.23, 2.82)	0.748			
Yes	-	-	-	-	-	-
Anemia						
No	0.58	(0.18, 1.87)	0.362			
Yes	-	-	-	-	-	-
Age	0.97	(0.90, 1.05)	0.453			

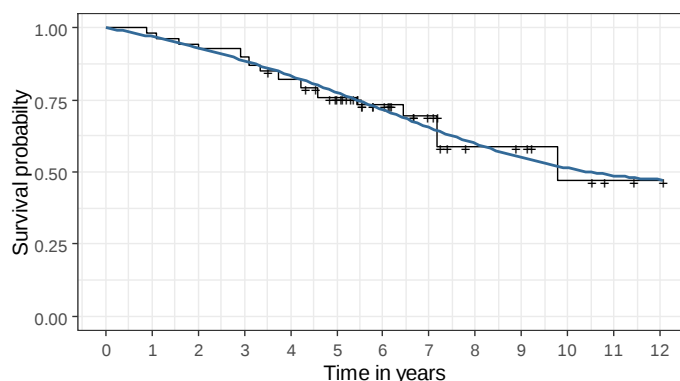


Figure 1. Overall survival plot; the step diagram indicates Kaplan-Meier estimation and the blue line represents the Marshall-Olkin gompertz fit

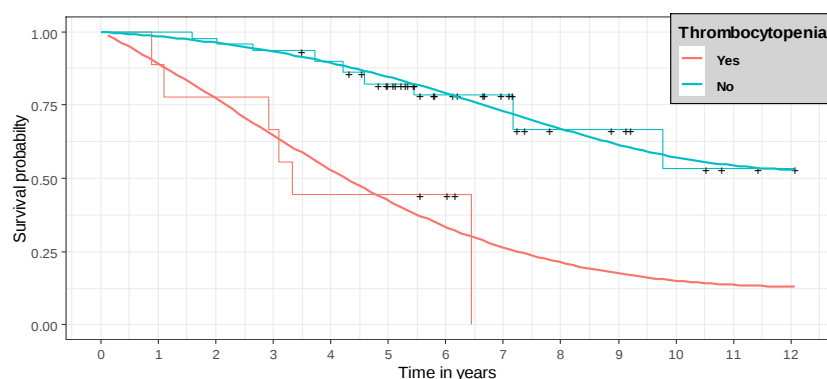


Figure 2. Overall survival based on thrombocytopenia at diagnosis. The step diagrams indicate Kaplan-Meier estimation and smooth curves represent Marshall-Olkin gompertz fit for the two categories

4. Discussion

Generally, multiple myeloma patients have a 5-year survival rate between 40% and 82%, which is in line with

this study's findings [13]. According to previous studies, pre-transplant thrombocytopenia is a risk factor for allogeneic hematopoietic stem cell transplantation (allo-HSCT) [14]. In the present study, an assessment

of the impact of blood factors in the first CBC test was made on the outcome of patients with MM undergoing autologous stem cell transplantation. A low Plt count was associated with a substantially lower chance of survival ($p = 0.005$). We found insufficient statistical evidence regarding the OS despite the fact that low Hb is associated with poor quality of life, cardiovascular problems, hypoxia, and ischemic complications in MM patients [15]. According to previous studies, in both treatment responsiveness and survival, anemia does not appear to have an impact [16].

Age is known as a highly significant prognostic factor for MM due to the higher tolerability of high-dose therapies in younger patients; however, age distribution was limited in our study, so we did not detect a significant effect. In previous studies of MM survival, aging beyond 70 years was highly predictive of survival [17,18].

Modern cancer studies no longer assume that cancer survival curves will eventually reach zero since a substantial fraction of patients is being cured or living as long as the average person. As a result, conventional methods such as Cox's proportional hazards are no longer appropriate [19,20]. It is critical to use appropriate models to obtain exact, unbiased, and reliable conclusions from cancer survival studies. This context presents a novel issue of using long-term survival (cure) models [21]. Herein, we utilized a defective distribution, which is an innovative method in survival analysis yielding more exact and reliable results. For more information please refer to [22–24]. As an alternative, we can use the mixture cure model, as shown by Usmani et al. in their study of examining clinical predictors of survival for multiple myeloma patients [25]; however, defective models are eminently superior in terms of precision and efficiency [22].

In case of MM, cure does not refer to complete eradication of the disease, as patients usually suffer from chronic complications. Consequently, we regarded cure as surviving long parallel with a normal population [26].

The results of this study can be further accurate by taking a larger sample size and also including cases from multiple medical centers.

5. Conclusion

This article is an application of a defective cure model with interval censored data to find prognostic factors from the CBC test at diagnosis of multiple myeloma patients who treated with auto-HSCT. In conclusion, it was found that thrombocytopenia at the time of diagnosis is a strong predictor of overall survival.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted following the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1401.438) 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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