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Original Article:
A Mixture Cure Model for Interval Censorship With a Change Point Based on Age Threshold in Hodgkin Lymphoma Patients After Stem Cell Transplantation

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Abstract

Introduction: Hodgkin Lymphoma (HL) is one of the most curable cancers. A bulk of studies have validated the benefits of Hematopoietic Stem Cell Transplant (HSCT) for patients with relapsed or primary resistant HL. This analysis aimed to identify an effective change point in patients' ages, the cure fraction before and after the change point, and significant prognostic factors on the cure fraction before and after the change point for such patients after HSCT in Iran.

Materials and Methods: In this retrospective cohort study, there were 156 patients with HL who underwent HSCT from 2007 to 2014 with 18 months of a follow-up in Tehran, Iran. The survival time was set as the time interval between transplantation and the recurrence of HL. Also, the change point and the cure fraction before and after the change point were estimated using the Bayesian estimation method and log-normal distribution.

Results: Out of 156 individuals with HL who underwent stem cell transplantation, 77(49.4%) were male, and 79(50.6%) were female with the Mean±SD age of 30.3±8.99 and 29.3±8.16 at the time of transplantation, respectively. The estimated cure fraction was 79.2% for all patients. The effective change point in age was 35 years, and the cure fraction before and after the change point was 84.5 % and 60.6%, respectively. The best subset of variables related to the model in question include White blood cells and Hemoglobin; none of these variables were statistically significant before and after the change point.

Conclusion: The study concluded that the age of 35 years is a significant change point in age at the time of transplantation. If individuals undergo HSCT with HL before the age of 35, they have a higher survival rate (recurrence of HL) than those who do so afterwards.

Keywords: Hodgkin lymphoma, Mixture cure model, Change point, Interval censorship, Bayesian method

Introduction

Hodgkin Lymphoma (HL) is an unusual malignancy of lymphocytes, characterized by cancerous Reed-Sternberg cells in an inflammatory backdrop [1]. HL has a low and approximately stable incidence. Worldwide, in 2020, HL ranked as the 27th most common cancer, accounting for 0.43% of all new cancer cases (approximately 83,087 cases), and 23,376 individuals died of this cancer

[2]. During the same period in Asia,HL ranked as the 26th most prevalent cancer, comprising 0.33% of all new cancer cases (approximately 31,742 cases), and leading to the death of 11,079 individuals [3]. In Iran, in 2020, HL was the 19th most common cancer, accounting for 1.1% of all new cancer cases (approximately 1406 cases), and 511 individuals died of this cancer [4].

Luckily, approximately 85%-90% of patients achieve a complete remission with the conventional combination of chemotherapy and radiation therapy [5]. However, 10-15% of patients with relapsed or refractory disease will suffer from HL, notwithstanding the high first-line cure rates [6].

Individuals with relapsed or refractory HL who are not cured with first-line therapy could frequently be cured with autologous (auto-HSCT) or allogeneic hematopoietic stem cell transplantation (allo-HSCT). Currently, high-dose chemotherapy (HDCT) followed by auto-HSCT is the usual therapeutic procedure for individuals with refractory or relapsed HL [7, 8].

In recent studies, Hematopoietic Stem Cell Transplantation (HSCT) has been considered as one of the best therapeutic choices in several virulent diseases for achieving prolonged survival and reducing transplant-related fatality [9, 10]. In Iran, HSCT usage, compared to the last decade, has increased by ten times [11]. In spite of that, recurrences occur primarily within one to three years following HSCT [12].

Maintenance therapies are frequently assumed to be advantageous to reduce the danger of recurrence in patients with HL following HSCT. It is crucial to manage such patients since they are often young, without medical comorbidities, and can tolerate additional therapies. Consequently, the expectations of achieving a cure are high [13]. In survival data, time T may only be known to have occurred within an interval [a, b]. Thus, the time to an event of interest can be an interval censorship observation [14].

In recent years, the total survival trend of cancer patients has increased due to medical betterments in treatment. Therefore, a proportion of the population of patients may not be susceptible to the event of interest. These individuals are considered cured or non-susceptible patients [15].

Consequently, the population under study is considered a composite of cured and susceptible patients. Using the standard parametric and non-parametric survival models to estimate the parameters may be unsuitable due to heterogeneity within the population of patients. Thus, the application of the mixture cure model is more suitable than the classical survival models [16].

It is assumed that all variables have a stable effect on the total survival trend. Nonetheless, analyzing the real data indicates the deviation from this assumption, leading to the change point issue [17].

Specifically, we are interested in whether statistical evidence of the change point is based on an age threshold of HL Patients after stem cell transplantation. Identifying a change point has many benefits including improving treatment planning, helping guide resource allocation, etc. [18].

Prevention of disease recurrence following HSCT in patients with resistant or relapsed HL has recently been an area of unmet medical need. This analysis aimed to identify an effective change point in patients' ages, the cure fraction before and after the change point, and significant prognostic factors on the cure fraction before and after the change point for these patients after HSCT in Iran.

Materials and Methods

In this retrospective cohort study, the data of 156 patients were extracted for this analysis after deleting subjects with incomplete data. Patients with HL were referred to Taleghani hospital, affiliated with Shahid Beheshti University of Medical Sciences. After the initial treatment, the patients were treated with HSCT at the department of bone marrow transplantation, from 2007 to the end of 2014, with a follow-up of 18 months. The follow-up time was considered to determine the survival status of the patients contacted by telephone, whose survival situations were recorded from March 2015 to August 2016. If the patients had died, the cause and date of death were recorded; if the patients were alive, the research center staff informed that they would be pleased to invite them for re-examination.

Standard eligibility criteria included ages of less than or equal to 60 for allo-HSCT and less than or equal to 70 for auto-HSCT along with suitable function in cardiac, pulmonary, and hepatic organs.

The Patients' information in this study included gender, age at the time of transplantation, platelet (PLT), White Blood Cells (WBC), Body Surface Area (BSA), Hemoglobin (Hb), the type of stem cell transplantation (autologous or allogeneic), the Mononuclear Cells (MNCs), patients' experience of recurrence before HSCT, and sur-

vival status and survival time by days. The event variable was defined as recurrence of the disease; thus, the survival time was calculated based on the difference between the time of HSCT and the recurrence of the disease.

As a consequence of recent advancements in therapies, a high proportion of patients are expected to be cured. They remain disease-free after prolonged follow-ups. Hence, we use the mixture cure model because, in the mixture cure model, it is assumed that the study population consists of two groups, the first group of susceptible individuals and the second group of cured individuals [19]. In cancer studies, a long plateau of the Kaplan-Meier curve accompanied by reasonable follow-up time suggests a helpful usage of the mixture cure model.

Statistical analysis methods

In this article, we obtain all inferences and estimates using the Bayesian method. Therefore, to compare the different distributions and get the best distribution for the survival function of susceptible individuals among all the distributions (Weibull, Exponential, Log-normal, etc.), we use the deviance information criterion (DIC). Low value of the measure DIC indicates that the model is better [20]. After performing this method, it was determined that the best distribution for our data is the log-normal distribution. For this reason, only the results of this model will be presented in the continuance of the article.

Descriptive statistics Mean±SD for quantitative variables and number and percentage for categorical variables were used to summarize demographic and prognostic variables in the study of the population. We utilized the stepwise variable selection to identify the best subset of variables associated with the mixture cure model through the analysis before and after the change point.

In this study, we have tried to keep patients' secrets, and all ethical considerations have been observed (Code: IR.SBMU.RETECH.REC.1396.966). All statistical analyses were performed by SAS software version 9.4 (with the command: proc MCMC) and R software version 3.6.0 (with package: Survival), at an error level of 0.05.

Results

Out of 156 individuals with HL who underwent stem cell transplantation, 77(49.4%) were men, and 79(50.6%) were women with the Mean±SD age of 30.3±8.99 and 29.3±8.16 at the time of transplantation, respectively.

Before the HSCT, 66.0% of the patients experienced at least one relapse; however, after HSCT, 21 out of 156 patients (13.5%) experienced the recurrence of HL. For these uncured patients, the mean survival time was 999 days (95% Confidence Interval [CI]: 843-1155). Table 1 represents the results of descriptive statistics of the subjects based on age (year), BSA (m^2), MNC (count), Hb (g/dl), sex, the experience of pre-transplantation relapse, type of HSCT, WBC (mm^3), and PLT (mm^3), and Table 2 represents the descriptive statistics in recurrence and non-recurrence patients.

Conforming to Figure 1, for HL patients after HSCT and recurrence as the event of interest, the three and five-year survival rates were 82.1% (95%CI: 73-92) and 80.0% (95%CI: 70.5-90.5), respectively. It is visible that a large proportion of the patients had not experienced the recurrence within approximately four years after HSCT.

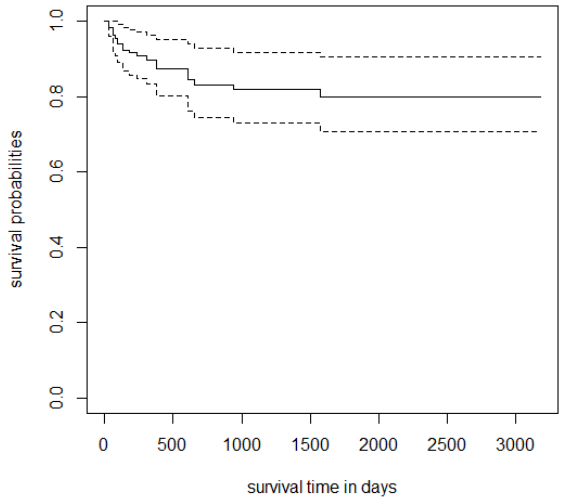

Figure 1. Kaplan-Meier survival curve of the whole study population with 95% confidence interval

Table 1. Descriptive statistics for categorical variables and numerical variables in all patients, before and after the change point

Variables		Mean±SD/No. (%)		
		All Patients	Age <35 years	Age ≥35 years
Age (y)		29.79±8.57[a]	26.11±4.77	43.03±5.56
BSA (m^2)		3.50±0.88	3.45±0.92	3.69±0.73
MNC (count)		5.85±1.45	5.89±1.39	5.72±1.68
Hb (g/dl)		9.34±0.88	9.33±0.89	9.39±0.89
Sex	Male	77(49.4)[b]	59(48.4)	18(52.9)
	Female	79(50.6)	63(51.6)	16(47.1)
Experience of relapse	YES	103(66.0)	80(65.6)	23(67.6)
	NO	53(34.0)	42(34.4)	11(32.4)
Type of transplantation	Autologous	144(92.3)	115(94.3)	29(85.3)
	Allogeneic	12(7.7)	7(5.7)	5(14.7)
WBC (mm^3)	WBC≤6797	100(64.1)	82(67.2)	18(52.9)
	WBC>6797	56(35.9)	40(32.8)	16(47.1)
PLT (mm^3)	PLT≤54,638	100(64.1)	76(62.3)	24(70.6)
	PLT>54,638	56(35.9)	46(37.7)	10(29.4)

a Mean±SD, b Number of patients (percent), MNC: Mononuclear cells, BSA: Body surface area, Hb: Hemoglobin, WBC: White blood cells, PLT: Platelet.

We are interested in whether an analysis that allows for the change point could clarify further information about the relationship between age at transplantation and Hodgkin's lymphoma survival. Also, for estimation of the cure fraction, we fitted a mixture cure model with a change-point based on the age threshold of patients with a log-normal distribution for the survival function of susceptible individuals.

After HSCT, the cure fraction was 79.2% (95%CI: 69.4, 86.7) for all patients (no change point), which indicates that approximately 80% of patients do not expe-

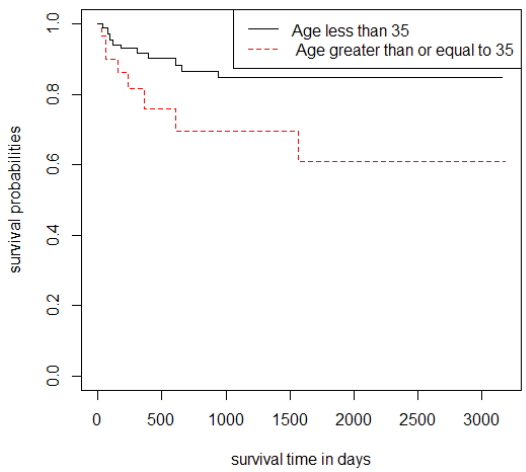

Figure 2. Kaplan-Meier survival plot for patients less than 35 years old and greater than or equal to 35 years old

Table 2. Descriptive statistics for categorical variables and numerical variables in recurrence and non-recurrence patients

Variables		Recurrence Patients	Non-recurrence Patients
Age (y)		32.05±9.55[a]	29.44±8.39
BSA (m^2)		3.44±0.83	3.51±0.89
MNC (count)		5.81±1.30	5.86±1.48
Hb (g/dl)		9.22±1.03	9.36±0.86
Sex	Male	10(47.6)[b]	67(49.6)
	Female	11(52.4)	68(50.4)
Experience of relapse	YES	17(81)	86(63.7)
	NO	4(19)	49(36.3)
Type of transplantation	Autologous	20(95.2)	124(91.9)
	Allogeneic	1(4.8)	11(8.1)
WBC (mm^3)	WBC≤6797	10(47.6)	90(66.7)
	WBC>6797	11(52.4)	45(33.3)
PLT (mm^3)	PLT≤54,638	12(57.1)	88(65.2)
	PLT>54,638	9(42.9)	47(34.8)

[a]Mean±SD; [b]Number of patients (percent); MNC: Mononuclear Cells, BSA: Body Surface Area; Hb: Hemoglobin, WBC: White Blood Cells, PLT: Platelet.

rience recurrence disease after HSCT; these individuals are considered cured or non-susceptible patients.

The change point amount in this study was estimated at 35.09 years with a standard deviation of 2.04(95%CI: 33.05, 37.13). The cure fraction was estimated to be 84.5% (95%CI: 73.7, 91.3) before the change point and 60.6% (95%CI: 35.5, 80.8) after the change point. Consequently, the patients with transplantation age younger than 35 years (change point) had better survival and higher cure fraction than those at the transplantation age of 35 or older. As shown in Figure 2, the difference between two cure fractions in patients could be considered as evidence of the existence of an effective change point at transplantation age.

The best subset of variables related to the model in question, parameter estimates, and 95% highest posterior density interval (HPD interval) for these variables both before after the change point are provided in Table 3 and Table 4, respectively. In the Bayesian method, if zero is in the 95% HPD interval, that variable is not significant,

Table 3. Parameter estimates based on the Bayesian method before the change point

Variables	Estimate (β)	Odds Ratio (e^{β})	SD[b]	95% HPD[c] Interval for
μ	5.50	-	0.33	(5.17, 5.83)
σ^2	1.42	-	0.38	(1.04, 1.80)
Constant	-0.68	-	1.58	(-2.26, 0.9)
WBC (WBC≤6797)[a]	1.29	3.63	1.50	(-0.21, 2.79)
Hb	0.17	1.18	0.50	(-0.33, 0.67)

[a]Reference category; [b]Standard deviation; [c]Highest Posterior Density; [μ]Mean parameter of Log-normal distribution; [σ2]Variance parameter of Log-normal distribution; WBC: White blood cells; Hb: Hemoglobin.

Table 4. Parameter estimates based on the Bayesian method after the change point

Variables	Estimate (β)	Odds Ratio (e^{β})	SD[b]	95% HPDc Interval for
μ	5.56	-	0.37	(5.19, 5.93)
σ^2	1.71	-	0.71	(1.00, 2.42)
Constant	-0.42	-	1.73	(-2.15, 1.31)
WBC (WBC≤6797)[a]	0.24	1.27	1.15	(-0.91, 1.39)
Hb	0.03	1.03	0.40	(-0.37, 0.43)

[a]Reference category; [b]Standard deviation; [c]Highest Posterior Density; [μ]Mean parameter of Log-normal distribution; [σ2]Variance parameter of Log-normal distribution; WBC: White Blood Cells; Hb: Hemoglobin.

and contrariwise. Thus, none of the variables in Table 3 and Table 4 are statistically significant. If the variable is significant, the variable is interpreted as odds ratios.

Discussion

Even though many risk factors have been described for HL patients relapsing after first-line treatment, reliable risk factors are still needed for those undergoing HSCT. Once the recurrence of HL was regarded as the event of interest, we found that the cure fraction is 79.2%(95%CI: 69.4, 86.7) for all patients, and the 3- and 5-year survival rates are 82.1%(95%CI: 73 - 92) and 80.0%(95%CI: 70.5 - 90.5), respectively.

The curable advantage of HSCT, followed by auto-HSCT in patients with resistant or relapsed HL, is supported by two studies in the literature. In the British National Lymphoma Investigation research, the statistical 3-year event-free survival is 53%, and freedom from the therapy failure rate in the German Hodgkin Study Group (GHSG), reported collectively with the European Group for Blood and Marrow Transplantation, has been assumed 55% [21]. In Iran, the 3-year disease-free survival is 77%(SE 3.7%) for HL patients by investigating stem cell transplantation with 20 years of experience [11].

In medical applications, the grouping of continuous variables such as age can make diagnosing and selecting the suitable treatment easier. Hence, the most important goal of this study is to obtain an effective change point in the age threshold of patients with HL. Group ages 20 to 34, forming almost one-third of new diagnoses, are the most common in HL patients [22].

In our study, where approximately 80% of the subjects were below 35 (change point), the analysis recognized the importance of age in how these patients have considerably higher cure fractions. Thus, patients under 35 years of age have about 24% higher cure fraction than patients greater than or equal to 35.

In 2020, Talleur et al. demonstrated the significant improvement of outcome in 74 young patients with resistant or relapsed HL after auto-HSCT over time [23].

However, pediatric patients have the same outcome as adults. In a case-matched group of 81 adult patients who had undergone HSCT, the Progression-Free Survival (PFS) rate was not significantly different between the age groups [24].

In contrast, extending the follow-up time to 20 years, in the study by Majhail et al., the advanced age was reported as an unfortunate outcome of HL patients after HSCT [25]. In the retrospective analysis by GHSG, ages higher than 45 had been identified as one of the adverse prognostic factors and low Hb and advanced stage of HL for tumor control [26].

The International Prognostic Score (IPS-7) serves as one of Hodgkin's lymphoma's most broadly risk stratification index. According to this index, ages higher than 45 years are independently associated with a more unsatisfactory outcome of HL [27]. These findings, aligned with our results, clarify the importance of age in patients with HL as they all emphasize the adverse effects of high age on the cure fraction of HL patients.

Nevertheless, in the aforementioned researches and many other pieces of research that have divided the age of patients with HL into two categories, it has been based on clinical and medical observations, but this paper used a robust statistical model such as the change point model to find the change point in patients' ages. We used powerful estimation methods such as the Bayesian method to estimate the model parameters. To the best of our knowledge, this is the first study to discover the change point

in the age at transplantation patients with HL statistically and accurately. Moreover, in this study, none of the studied variables significantly affected the cure fraction before and after the change point, which can be one of the important reasons for the small sample size.

The second novation of our research is the existence of interval censorship data, which is much more complex than right and left censorship. Most researchers ignore this type of censorship and prefer to use right-censorship because it is easier to analyze.

The primary limitation of our study was the rare number of HL patients who underwent HSCT. This limitation might be due to the rareness of the disease and a high initial cure fraction of first-line treatment. The Bayesian method was used to estimate the parameters in this research, and future researches can use other methods.

Conclusion

This article is an application of a mixture cure model for interval censorship with a change point based on age threshold on Hodgkin Lymphoma Patients after Stem Cell Transplantation. The study concluded that the age of 35 years is a significant change-point in the age of transplantation. If individuals underwent HSCT before the age of 35, they have a higher survival rate than those who underwent HSCT after 35. Also, none of the studied variables significantly affected the cure fraction either before or after the change point.

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.1396.966) and informed consent was obtained from all the patients.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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