RESEARCH ARTICLE

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Prognostic Factors for the Long-Term Survival after Hematopoietic Stem Cell Transplantation in Patients with Hodgkin Lymphoma

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Abstract

Objectives: This study investigated the possible prognostic factors for the long-term survival (Cure Rate) of Hodgkin Lymphoma patients who underwent HSCT. **Methods:** This retrospective cohort study analyzed 116 Patients diagnosed with Hodgkin Lymphoma who received autologous hematopoietic stem cell transplantation (Auto-HSCT) between the years 2007 and 2014 and followed up until 2017. The information regarding patients' survival had been collected using phone calls, and their pre-transplant information was available in the archived documents. Prognostic effects were investigated using long-term survival models. **Results:** Patients with obesity had five times higher odds of long-term survival (cure) than the others (P=0.06). Also, the recurrence experience after HSCT negatively impacted the curing potential by 78% (P=0.05). Also, with 32 years as the change point, patients younger than 32 had 76% fewer odds of surviving long-term (P=0.03), and Poor transfused stem cell dose of CD34+ ($<0.16 \times 10^6$ cells/ml) reduced the odds of long-term survival by 92% (P=0.01). **Conclusion:** According to the statistical models used in this study, obesity can increase the curing potential of Hodgkin lymphoma after transplantation. Meanwhile, aging, poor transfused CD34+ cells, and recurrence after HSCT were associated with lower survival following HSCT.

Keywords: Hematologic neoplasms- Hodgkin Lymphoma- survival analysis- cure rate

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Introduction

Hodgkin lymphoma (HL) is a rare B-cell malignant neoplasm affecting approximately 9000 new patients annually (Ansell, 2015). The first line treatment for Hodgkin lymphoma, based on the histologic characteristics, is chemotherapy in combination with immunotherapy and radiation therapy (Evens et al., 2008). At present, more than 80% of newly diagnosed patients are expected to be long-term survivors, according to current treatments (Liu et al., 2017). But mortality is still high in refractory patients and non-Hodgkin lymphoma (von Tresckow and Moskowitz, 2016).

Salvage chemotherapy and high-dose treatment followed by an autologous stem cell transplant is the standard of care in patients with relapsed or refractory disease (Gross et al., 2010). Autologous stem cell transplantation (ASCT), as compared to salvage chemotherapy in patients with relapsed, chemotherapy-sensitive Hodgkin and non-Hodgkin lymphoma (NHL), has been shown to be a superior modality of therapy in terms of progression-free survival (PFS) and overall survival (OS) that allows for approximately 30-65% cure for these patients (Gordan et al., 2003). However, some published studies have integrated different factors such as the chemotherapy courses before Hematopoietic stem cell transplantation (HSCT), age, BMI, performance status, laboratory abnormalities, and extra nodal involvement, increase the risk of recurrence within one to three years after HSCT (Satwani et al., 2015; Castagna et al., 2016).

In recent years, advances in cancer treatment have led to extensive statistical research to develop models of long-term survival (Othus et al., 2012). The classical survival models assume that everyone will eventually face the event of interest. In contrast, long-term survival models (cure models) take into account long-term survivors who may not have experienced it (Maller and Zhou, 1997). The remarkable point is that when there are such event-immune cases in the study, standard survival models such as standard Cox's proportional hazards are inappropriate and

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could lead to biased results (Amico and Van Keilegom, 2018). Moreover, the simplest way to examine whether a data set contains a subset of long-term survivors is to have a quick look at the survival curve. Hence, if a plateau is present at the end of the survival curve, there might be a cure fraction in the study, and the survival value of the plateau indicates the estimated percentage of long-term survivors. Cure models come in two major forms: mixture and non-mixture, with mixture models being the usual approach which separates the immune and susceptible part of the subjects (Othus et al., 2012).

This study aimed to compare the cure rates for lymphoma patients undergoing HSCT along with an interpretation of common risk factors.

Materials and Methods

In this retrospective cohort study, we modeled survival time for HL patients who underwent autologous hematopoietic stem cell transplantation (Auto-HSCT) at the department of HSCT in Taleghani Hospital, supervised by Shahid Beheshti University of Medical Sciences, Tehran, Iran. A list of patients who were nominated for HSCT from 2007 to 2014 was followed through 2016. The recorded information was used to confirm whether the patients were still alive. Moreover, a notable number of cases (19.4%) were eliminated due to incomplete information; Thus, eventually 116 cases were included in the study. There were numerous factors that were present in our data set, including gender, age, BMI, relapse before HSCT, recurrence after HSCT, white blood cell count, hemoglobin and platelet count prior to HSCT and the number of mononuclear cells and CD34+ cells present in transfused stem cells. As the required information was recorded through available documents and no interventions were performed, this study had no ethical issues.

Statistical Analysis

The survival function for a mixture model is defined as $S(t) = p + (1-p)\, S_0(t)$, where p represents the cure rate and S_0 (t) corresponds to a conventional survival function (Boag, 1949; Berkson and Gage, 1952). A superior way of long-term survival modeling is to use non-mixture cure model which does not rely on segregation. In this model, survival is defined by $S(t) = p^{1-S0(t)}$; Again, p denotes the cure rate and S_0 (t) is a traditional survival function (Tsodikov et al., 2003; Achcar et al., 2012).

In order to intuitively evaluate survival differences and the existence of cure fractions, Kaplan-Meier (K-M) survival curves were used. We fitted both mixture and non-mixture models using the Generalized Modified Weibull (GMW) family of distributions (Carrasco et al., 2008) as the baseline survival. Moreover, for categorizing continuous variables, we determined the best change point through fitting a non-mixture GMW model -the most complicated model- and successively dichotomizing the continuous variable at each possible cut point, then selecting the cut point with the highest likelihood. Further, Influential factors to the cure rate selected using Purposeful variable selection approach introduced by Hosmer et al., 2011. Then, we provided a comparison for those models in terms of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Lee and Wang, 2003). Lower values indicate a better fit. Therefore, the best fit was chosen for the best interpretation. P-values were all obtained from two-sided tests and computations and figures were provided in R version 4.1.2.

Results

38 patients (19.6%) died from 116 Hodgkin's disease cases undergoing HSCT. The mean survival time limited to the maximum was 6.68 years [95% CI: 6.07, 7.28□]. At the time of HSCT, the mean age was 29.61, with a standard deviation of 8.64. Table 1 provides summarized information about patients and their variables.

As shown in figure 1, the Kaplan-Meier survival curve for all patients in the survey (Blue curve) reaches a plateau at just under 75% after 5.5 years. The red curve represents a non-mixture GMW survival fit, which estimates a cure rate of 0.73 [95% CI: 0.387, 1.0].

Figure 2 shows the univariate survival fit as well as the empirical estimation (Kaplan-Meier) based on the following variables: age (a), CD34+ cell dose level (b), obesity (c), and recurrence after HSCT (d). For the first two variables, we analyzed survival change points, and it revealed that long-term survival chance dramatically changes at the age of 32. Conversely, patients with low CD34+ cell doses (less than 0.16×10^6 cells/kg) in their collected stem cells had a strikingly reduced chance of being long-term survivors.

In patients older than 32 years of age, the estimated cure rate was 0.56 [95% CI: 0.20, 0.92], whereas, in those younger than 32 years, it was 0.80 [95% CI: 0.464, 0.920]. The difference between those cure rates was

Table 1. Patients' Characteristics

Variable	Frequency	Percentage
Survival Status		
Died	19	16.4
Right Censored	97	83.6
Gender		
Male	56	48.3
Female	60	51.7
Obesity		
Yes	30	25.9
No	86	74.1
Relapse before HSCT		
Yes	79	68.1
No	37	31.9
Recurrence after HSCT		
Yes	14	12.1
No	102	87.9
CD34+ Cells		
$\leq 0.16 \times 10^6$ cells/kg	10	8.6
$> 0.16 \times 10^6$ cells/kg	106	91.4

HSCT, Hematopoietic Stem Cell Transplantation

Table 2. Comparison of Parametric Fits

Baseline Survival		Model			
		Non-Mixture		Mixture	
Distribution	Number of Parameters	AIC	BIC	AIC	BIC
Exponential	1	56.18	72.701	57.931	74.453
Generalized Rayleigh	2	57.762	77.037	59.187	78.462
Exponentiated Exponential	2	58.081	77.356	59.824	79.099
Weibull	2	58.115	77.39	59.891	79.166
Modified Weibull	3	59.272	81.301	60.977	83.006
Exponentiated Weibull	3	59.326	81.355	60.739	82.768
Generalized Modified Weibull	4	61.851	86.474	62.59	87.372
Rayleigh	1	70.366	86.887	74.302	90.823
Extreme Value	2	71.993	91.268	75.103	94.378

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

statistically significant (P=0.0347). Moreover, cure rates were estimated at 0.25 [95% CI: 0.0, 0.642] and 0.78 [95% CI: 0.466, 1.0] for patients with lower CD34+ cell dose and otherwise, with a highly significant difference (P=0.0076). In obese patients, the cure rate was higher: 0.83 [95% CI: 0.449, 1.0] compared to 0.57 [95% CI: 0.172, 0.967] (P=0.0701). In addition, those who recurred after HSCT had a 0.42 [95% CI: 0.032, 0.827] cure rate, while those without recurrence had a 0.78 [95% CI: 0.425, 1.0] cure rate, with a significant difference between two groups (P=0.0207). Finally, other variables showed no significant survival difference at all.

Table 2 summarizes the performance of mixture cure models as well as non-mixture cure models based on the GMW family of distributions. All in all, the exponential distribution yielded the best results under non-mixture formulation, as the AIC and BIC had the least values (56.18 and 72.7, respectively). It is evident that non-mixture models performed better with all members of the GMW family of distributions. According to the Non-Mixture Exponential model, we identified the results outlined in Table 3.

The multiple model fit shows that obesity might have some effect on the cure rate, so that after adjusting for other variables, obese patients have more than five times higher cure rate than those with a lower BMI. Also, Patients with recurrence after HSCT had 0.78 fewer odds of being long-term survivors than those without recurrence. Expectedly, the age of patients affected the cure rate, and it was estimated that patients younger than 32 had 0.76 fewer odds of surviving long-term than younger patients. Furthermore, poor CD34+ cell dose in the transfused stem

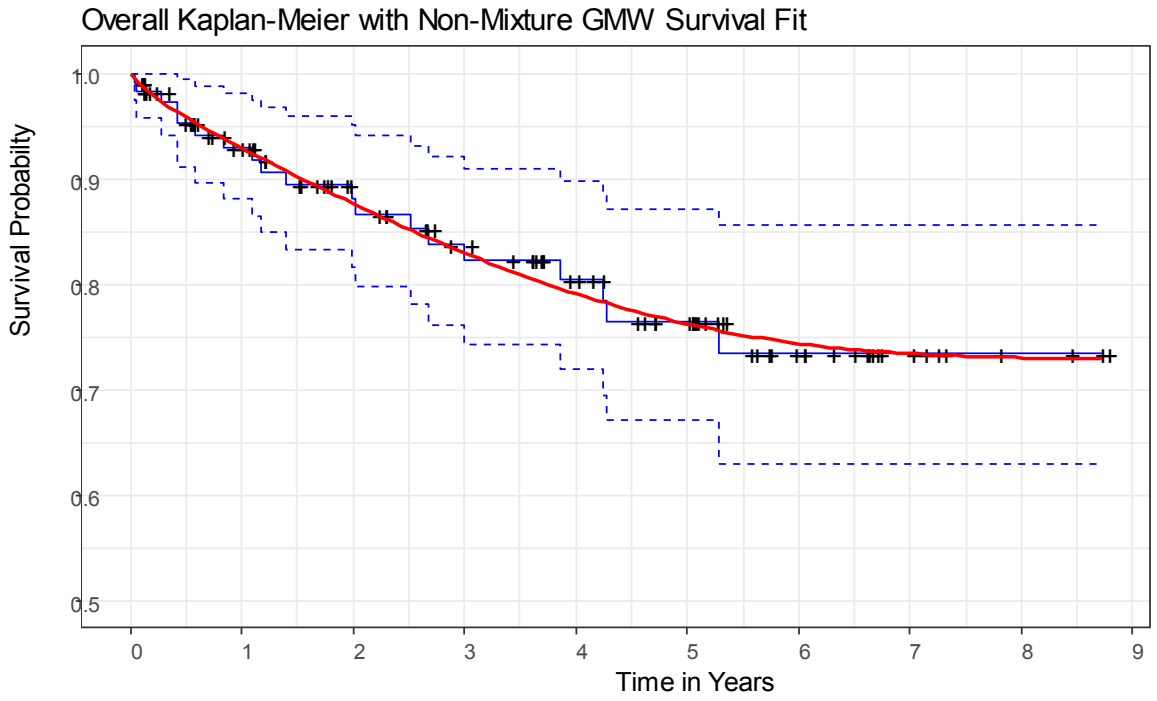

Figure 1. Overall Survival Rate of Hodgkin Lymphoma Patients in the Study with a 95% Confidence Interval (Blue curves) Accompanied by Non-Mixture GMW Survival fit (Red curve). (Overall Cure Rate = 73%)

Table 3. Output

Factor	Estimate	SE	P-value	OR	95% CI
Intercept	1.11	0.892	0.2138	-	-
Obesity					
Yes	1.633	0.9	0.0696	5.12	(0.877, 29.931)
No	-	-	-	-	-
Recurrence after HSCT					
Yes	-1.523	0.784	0.052	0.22	(0.047, 1.017)
No	-	-	-	-	-
Age					
> 32	-1.427	0.681	0.0362	0.24	(0.063, 0.912)
≤ 32	-	-	-	-	-
CD34+ Cells					
$\leq 0.16 \times 10^6$ cells/kg	-2.477	1.051	0.0185	0.08	(1.011, 0.659)
$>0.16 \times 10^6$ cells/kg	-	-	-	-	-
Distribution Parameters					
alpha	1.202	1.077	0.2644	-	-

alpha is the single parameter of the exponential distribution.

cell was found to reduce the odds of long-term survival to an early death by 92 percent.

Discussion

A practical method of assessing cancer treatment progress is tracking patients' survival over time. There have been numerous studies on survival monitoring in various types of cancer. For instance, the following studies By Moamer et al., 2017 ; Baghestani et al., 2017 applied novel statistical models to analyze the survival of colorectal cancer. HSCT is a well-established approach to the treatment of patients with relapsed/refractory Hodgkin lymphoma, and reliable risk factors are still needed for them. We found that obesity, age of fewer than 30 years, and CD34 cell dose above 0.16×10^6 cells/ml are good

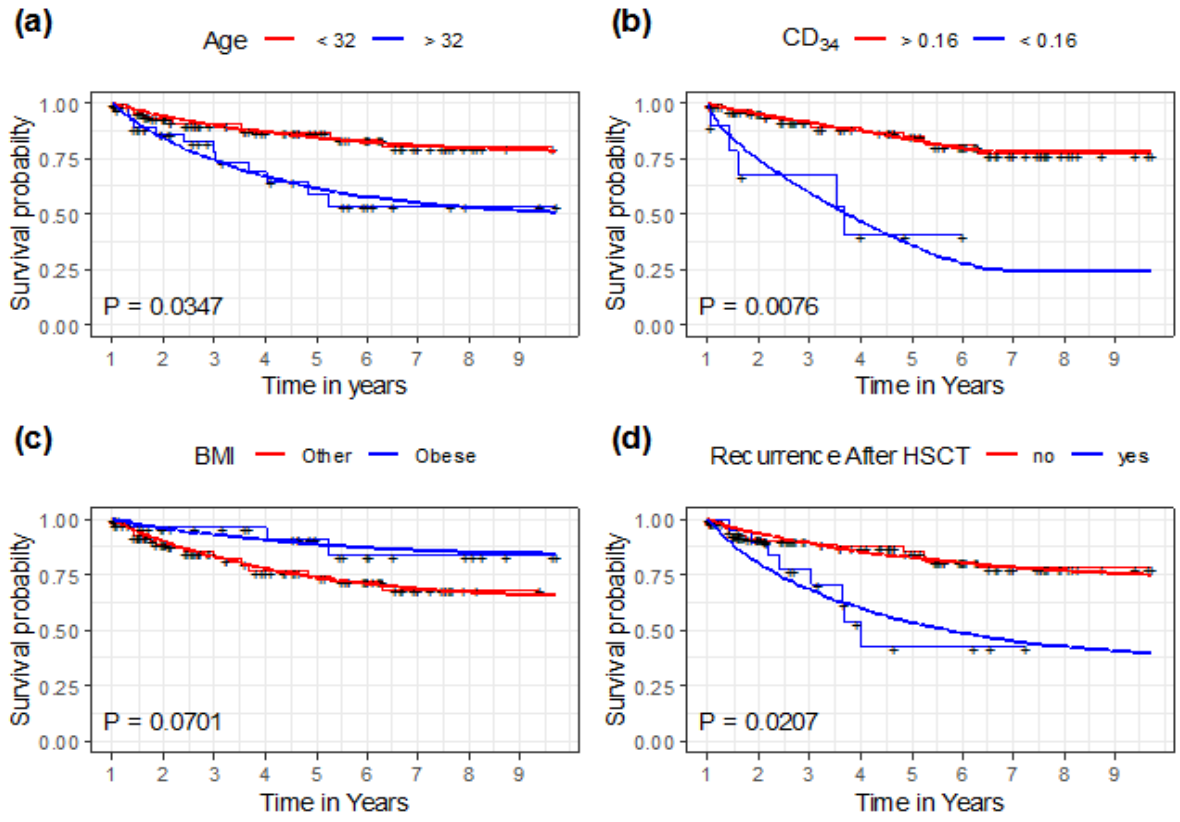

Figure 2. Univariate Survival Fit along with Its Empirical Estimation (Kaplan-Meier estimation) for the Significant Variables on the Long-Term Survival of Hodgkin's Disease.

prognostic factors for long-term survival in Hodgkin Lymphoma patients following HSCT.

A recent study by Tailleur et al. improved HSCT outcomes have significantly improved over time. Compared with patients treated in the earlier era (1988–2001), 5-year OS improved from 62.5 ± 9.6% to 91.8 ± 4.4% ($p < 0.001$), and Event free survival improved from 41.7 ± 9.6% to 87.7 ± 5.3% ($p < 0.001$) for patients treated in the most recent era (2002–2015) (Talleur et al., 2020). In European populations with Hodgkin's lymphoma, the 3-year event-free survival is 53%, and freedom from the treatment failure rate has been assumed to be 55% after HSCT (Josting et al., 2005; Kwan et al., 2017). The 3-year disease-free survival is 77% (SE 3.7%) for HL patients undergoing HSCT in the Iranian population (Ghavamzadeh et al., 2013). Overall, many studies improved the success of Auto-HCT for relapsed or refractory HL patients in recent years, but prognostic factors influence this success before and after HSCT.

The overall rate of HSCT failure in older patients is higher than in young adults because of comorbidities, impaired health, and performance status. (Duarte and Sánchez-Ortega, 2018; Brice et al., 2021). Akhtar et al. demonstrated 5-year overall survival and event-free survival almost the same in adolescents (14–21 years) compared to young adults (>21–30 years) (Akhtar et al., 2016). In our study, the age range of the patients was 20 to 60 years, and our results showed that age 32 could be a determining age in post-transplant survival and improved the cure rates, which was higher in patients 32 years old compared to those younger than 32 years old (P=0.0347). Some studies improved HSCT outcomes in elderly patients, but in this group of patients, due to low performance and comorbidity, fewer candidates receive transplantation (Basak et al., 2016).

It is found that having recurrence after HSCT exacerbates a patient's odds of being a long-term survivor, which is previously suggested by other studies (Kornacker et al., 2009). However, the p-value was just on the edge of significance.

A low CD34+ dose significantly reduces bone marrow transplant success. Several studies have shown that CD34+ cells can affect disease progression, but none have used statistical methods to pinpoint the change point (Sorigue et al., 2017; Balint et al., 2020). A study of 438 patients with non-Hodgkin lymphoma (NHL) or multiple myeloma (MM) confirmed the association of CD34+ transplant cell dose with better long-term recovery of platelets after ASCT that was associated with poor survival after HSCT (Stiff et al., 2011; Shimomura et al., 2018). One of the most recent studies on 141 patients who underwent autologous transplantation demonstrated that obese patients highly profit from high transplanted CD34 stem cell dosage for thrombocyte recovery due to the increased total transplanted CD34 cells numbers (Enßle et al., 2021).

Although there was not much significant evidence about the influence of obesity on the survival of Hodgkin's lymphoma patients, we consider it an advantageous factor in the cure rate of Hodgkin's lymphoma patients, in agreement with studies elsewhere (Navarro et al., 2006; Carson et al., 2012; Leo et al., 2014; Woodall et al., 2020). The inflated p-value is subject to high estimated variance due to insufficient sample size in the obese category. According to our results, patients with BMI ≥ 30 had significantly improved overall survival, and adverse events were not associated with differences in BMI.

As long-term survival data becomes more complex, especially in diseases such as cancer, it is desirable to use more flexible cure models. Numerous statistical studies have recently been conducted to develop superior cure models. (Balka et al., 2011; Amico and Van Keilegom, 2018; Martinez and Achcar, 2018; Baghestani and Hosseini-Baharanchi, 2019; Calsavara et al., 2019).

While the conventional method of analyzing long-term survival is the mixture cure model, a non-mixture cure model could yield a more preferred fit. Here, AIC and BIC were used to measure goodness-of-fit, and it was determined that non-mixture models outperformed traditional mixture models. Finally, new approaches, such as defective models, can further enhance this performance (Ferreira Da Rocha, 2016).

There were limitations in the current study. First, data were extracted by a statistical group. Second, the number of HSCT operations was limited. Achieving more will improve the results. Besides, data were collected from a single medical center; consequently, the results obtained in this study cannot be generalized to all patients with the same disease.

In conclusion, it is imperative to use a suitable model when analyzing survival data with long-term survivors. We need to use more flexible models in diseases such as cancer, which might have a complex hazard function. Hodgkin lymphoma is a broadly curable disease in which obesity and vigorous stem cell with a higher dose of CD34+ cells can significantly increase the treatment potential. In contrast, recurrence after HSCT and age are associated with a lower cure rate.

Author Contribution Statement

A collaborative effort among all authors has resulted in this work. D. Kadkhoda was the primary author and performed the analysis, wrote and reviewed the manuscript, and took part in study design, conceptualization, data gathering, and every section of the manuscript. M. Nikoonezhad took the primary part in writing clinical aspects of the manuscript and reviewed and conceptualized the study. A.R. Baghestani supervised and reviewed the statistical methodology. S. Parkhide was the clinical consultant. Z. Momeni-Varposhti took part in data gathering and writing the discussion and methodology. The main supervision, conceptualization, and final approval were done by A.A. Khadem Maboudi. All authors read and approved the final manuscript.

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Ethical confirmation

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the present study. (Code: IR.SBMU.RETECH.REC.1401.438)

Availability of data

The data that support the findings of this study are available from the corresponding author, A.A. Khadem Maboudi, upon reasonable request.

Conflicts of interest

There was no conflict of interest in this study.

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