Original Article
Middle East Journal of Cancer; July 2022; 13(3): 427-437

A Cure Rate Survival Model after Stem Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma Patients

Navid Mohseni*, MSc, Ali Akbar Khadem Maboudi*♦, PhD, Ahmadreza Baghestani*, PhD, Abbas Hajifathali, MD, Anahita Saeedi*, MSc**

*Department of Biostatistics, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
**Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Please cite this article as: Mohseni N, Khadem Maboudi AA, Baghestani A, Hajifathali A, Saeedi A. A cure rate survival model after stem cell transplantation for relapsed or refractory Hodgkin lymphoma patients. Middle East J Cancer. 2022;13(3):427-37. doi: 10.30476/ mejc.2021.88135.1461.

Abstract

Background: Hodgkin lymphoma (HL) is one of the best curable malignancies. Randomized controlled studies have validated the benefit of hematopoietic stem cell transplant (HSCT) for patients with relapsed or primary refractory HL. This analysis aimed to identify significant prognostic factors on the recurrence of the disease after HSCT applying a cure rate model.

Method: In this retrospective cohort study, there were 92 patients with HL who underwent HSCT from 2007 to 2014 with 18 months of follow-up in Tehran, Iran. The survival time was set as the time interval between transplantation and the recurrence of HL. In addition, we utilized hyper-Poisson distribution as discrete frailty to account the unobserved heterogeneity and random effects.

Results: In non-cured cases, the mean of survival time was 318 (95% confidence interval, 144-493) days. The 1-, 3-, and 5-year survival rates were 88.9%, 83.4%, and 80.7%, respectively. A significant association was observed between the cured patients and the variables such as age, the experience of pre-transplantation relapse, hemoglobin (Hb), mononuclear cells (MNCs), and body surface area (BSA) at the time of transplantation.

Conclusion: The study concluded that less than 30 years of age, a high level of Hb (g/dl), a low level of MNCs and BSA (m^2), and the absence of pre-transplantation experience of relapse were associated with better survival following HSCT. Based on this study, post-transplant consolidation therapies could be considered for the treatment of HL patients after HSCT.

Keywords: Hodgkin lymphoma, Survival analysis, Survival rate, Stem cell transplantation

♦Corresponding Author:
Ali Akbar Khadem Maboudi, PhD
Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti Medical University of Medical Sciences, Tehran, Iran
Tel: +9821-22707347
Email: amaboudi@sbmu.ac.ir

Introduction

Hodgkin lymphoma (HL), characterized with the presence of cancerous cells called Reed-Sternberg (RS) cells, is a rare malignancy with 0.4% of all new tumors and 0.3% of

Received: September 16, 2020; Accepted: May 01, 2021

all cancer deaths in 2018.[1] HL has a low and relatively stable incidence with slight male excess. Worldwide, the estimated age-adjusted incidence rates for 2018 were 1.1 and 0.8 per 100,000 males and females, respectively.[2] The rates vary internationally: the estimated 2018 incidence rates ranged from 2.3 and 1.8 per 100,000 males and females in more developed regions to 0.9 and 0.6 per 100,000 males and females in less developed regions.[1] In Iran, with approximately 1140 cases (accounting for 1% of all new cases), HL ranked as the 21st most common cancers in 2018.[3]

Since the treatment of HL over the past few decades has significantly increased the survival rate, most patients with HL are cured by first-line therapy in a way that currently more than 80% of newly diagnosed patients are expected to be long-term survivors.[4] In terms of mortality rate, after stomach cancer, the second statistically significant declination occurred in HL (decrease of 16.8% [14.0-19.8] to 0.4 deaths [0.4-0.5] per 100,000) in the decade of 2007-17.[5] Nonetheless, 10%-20% of patients with relapsed or refractory disease will suffer from HL despite the high first-line cure rates.[6] Patients with relapsed or refractory HL who are not cured with initial therapy could often be cured with autologous (auto-Hematopoietic stem cell transplantation (HSCT)) or allogeneic hematopoietic stem cell transplantation (allo-HSCT). Currently, high-dose chemotherapy (HDCT) followed by auto-HSCT is considered as the standard care for suitable patients with refractory or relapsed HL, which allows for approximately 30%-65% cure for these patients.[7-10] However, a subset of patients with a high risk of failure is a more compatible candidate for experimental procedures like allo-HSCT.[9]

HSCT is considered one of the best treatment options in several malignant diseases for achieving prolonged survival and reducing transplant-related mortality in recent studies.[11,12] In Iran, HSCT utilization, compared with the last decade, has increased by ten times.[13] Nevertheless, relapses occur mostly within one to three years following HSCT and risk factors for recurrence include a stage at relapse, the presence of B symptoms, the number of chemotherapy regimens given before auto-HSCT, performance status, laboratory abnormalities, and extranodal involvement. Different published studies have integrated different factors.[14-16] Maintenance therapies are often assumed to be beneficial to alleviate the risk of relapse for patients with HL following HSCT. It is particularly important to manage such patients since they are often young, without medical comorbidities, and can endure additional therapies. Therefore, the expectations of achieving a cure are high.

The cure rate model has been used to model time-to-event data, within which a significant proportion of patients are disease-free, who could be considered cured or insusceptible patients.[17] The survival time of cured individuals might be censored at the end of the follow-up study. Hence, if the follow-up time is long enough, there might be cured individuals in the dataset. This feature indicates models like classical survival models that ignore the possibility of cure will not be suitable enough.[18] Moreover, it is known that several other unknown factors can influence survival and cannot be included in the analysis, which may be due to the economic reasons or lack of appropriate knowledge. The concept of frailty suggests an appropriate way to account for unobserved heterogeneity and random effects in the data analysis of lifetimes.[19] Identification of HL patients with a high risk of relapse after HSCT is crucial for two main reasons: primarily, finding a subset of patients who would benefit from consolidation therapy; secondly, patients at low risk for relapse might be suitable for less exhaustive procedures. Prevention of disease recurrence following HSCT in patients with refractory or relapsed HL has recently been an area of unmet medical need. The present study aimed to investigate the cure rate and possible risk factors for these patients after HSCT in Iran.

Materials and Methods

Patients with HL referred to Taleghani hospital, which is affiliated to the Shahid Beheshti University of Medical Sciences. After the initial therapy, the patients were treated with HSCT at the department of bone marrow transplantation,

Table 1. Descriptive statistics for categorical variables and numerical variables

Variables	Total of patients	Patients who had recurrence
BSA (m^2)	3.42 ± 0.84*	2.99 ± 0.59
Hb (g/dl)	9.34 ± 1.46	8.88 ± 1.02
MNCs (count)	5.99 ± 1.57	5.54 ± 1.46
Age		
over 30	32 (34.8) **	7 (58.3)
below 30	60 (65.2)	5 (41.7)
Sex	44 (47.8)	5 (41.7)
Male	48 (52.2)	7 (58.3)
Female		
Type of transplantation		
Autologous	82 (89.1)	11 (91.6)
Allogeneic	10 (10.9)	1 (8.4)
Experience of relapse		
Yes	55 (59.8)	10 (83.3)
No	37 (40.2)	2 (16.7)

*Mean ± standard deviation; ** Number of patients (percent); BSA: Body surface area; Hb: Hemoglobin; MNCs: Mononuclear cells

from 2007 to the end of 2014, with a follow-up of 18 months. Standard eligibility criteria included age ≤ 60 for allo-HSCT and ≤ 70 for auto-HSCT along with appropriate function in pulmonary, cardiac, and hepatic organs. The patients' information in this study included sex, age at the time of transplantation, hemoglobin (Hb), body surface area (BSA), the mononuclear cells (MNCs), the type of stem cell transplantation (autologous or allogeneic), patients' experience of relapses before HSCT, and survival status and time by days. We dichotomized age variable into two age groups in order to compare the difference between the young adults (less than 30) and older adults (more than 30).[20-22] The follow-up time was considered to determine the survival status of the patients who were contacted by telephone, whose survival conditions were recorded from March 2015 to August 2016. If the patients 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. In this retrospective cohort study, after deleting the subjects with incomplete data and missing observation times, 92 cases were identified with HL from all the 122 HL patients, who underwent HSCT and the event variable was defined as recurrence of the disease; therefore, the survival time was calculated based on the difference between the time of HSCT and the recurrence of the disease.

As a result of recent advancements in treatment therapies, a high proportion of patients are expected to be cured. In other words, they remain disease-free after prolonged follow-ups. In cancer studies, a long plateau of Kaplan-Meier plot accompanied by reasonable follow-up time suggests a useful application of cure rate models. In order to account for the heterogeneity caused by unmeasured covariates, the frailty approach is commonly employed as an appropriate statistical modeling method. Each patient has their frailty and those with higher frailty are more prone to have the event earlier. Cured patients encompass zero frailty as there is a subgroup of non-susceptible individuals where the event of interest does not happen even after a long period of the observation period. In this situation, models induced by frailty with a non-negative and continuous distribution would not be proper anymore. Hence, discrete frailty is a need to model the cured patients accurately.[19-23] We focused on a flexible probability distribution induced by discrete frailty, hyper-Poisson distribution (hP), which is used for modeling count data characterized by over-dispersion or under-dispersion; in other words, an extra parameter (η) controls the heterogeneity. Flexibility of hP indicates that the equidispersion assumption of the Poisson regression model is

Table 2. hP cure rate for the risk factors in simple analysis

Variables	hP cure rate	*P*-Value
BSA (m^2)	0.826	<0.001*
Hb (g/dl)	0.808	0.008*
MNCs (count)	0.804	<0.001*
Age		
over 30	0.659	<0.001*
below 30	0.873	
Sex		
Male	0.816	0.019*
Female	0.792	
Type of transplantation		
Autologous	0.802	0.792
Allogeneic	0.807	
Experience of relapse		
No	0.907	<0.001*
Yes	0.732	

*Significance at the 10% level; BSA: Body surface area; Hb: Hemoglobin; MNCs: Mononuclear cells; hp: Hyper-Poisson distribution

not a limitation anymore.[24] Generally, the Weibull model could be an adequate alternative for baseline distribution with α and λ as shape and scale parameters, respectively. Descriptive statistics (mean ± standard deviation (SD)) for continuous and frequency for categorical variables were used to summarize demographic and prognostic variables in the study of the population. In addition to simple analyses, the multiple effect of variables on the survival time after HSCT were evaluated for clinical practicability. We utilized the stepwise variable selection to identify the best subset of variables associated with the hP cure model through the analyses. According to this method, variables with $P < 0.1$ were entered and those with $P > 0.2$ were removed from the analysis. 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

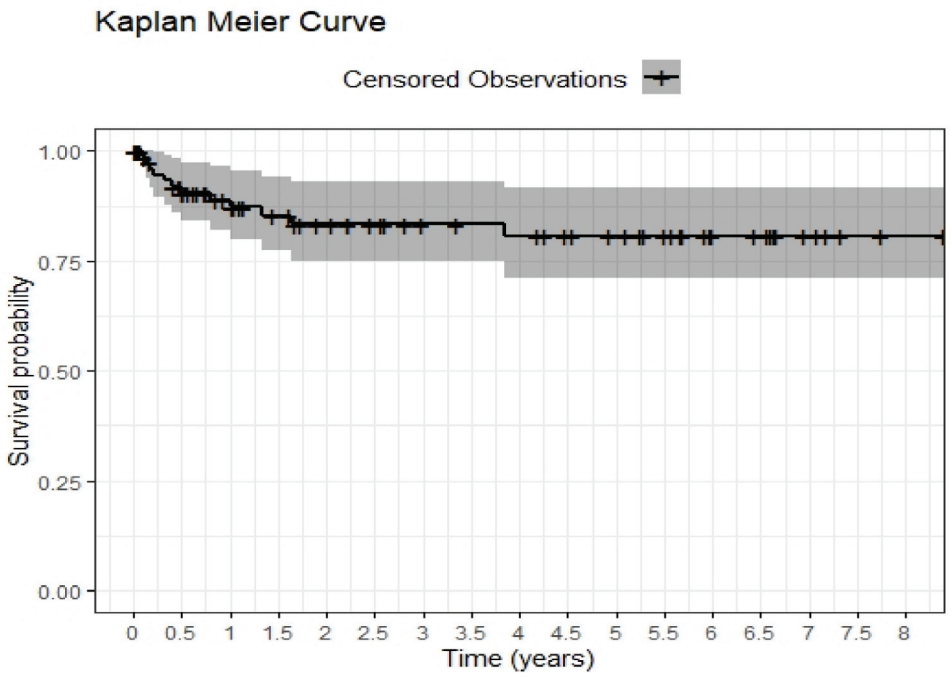

Figure 1. This figure shows the Kaplan-Meier survival curve for the entire study population with highlighted 95% confidence interval.

informed consent was obtained from all the patients. All the statistical analyses were performed with R programming language version 3.5.2 (packages: dplyr, ggplot2, survival, stats) and the $P < 0.1$ and $P < 0.05$ were considered as the level of statistical significance for single and multiple analyses, respectively.

Results

Out of 92 individuals with HL who underwent stem cell transplantation, 47.8% were men and 52.2% were women with the mean age of 29.5 (SD of 8.95), and 29.9 (SD of 9.38), respectively, at the time of transplantation. At the time of HSCT, 65.2% of our patients were over the age of 30 and 34.8% were under that age 30. Prior to HSCT, 59.8% of the patients experienced at least one relapse; however, after HSCT, 12 out of 92 (13%) of them experienced the recurrence of HL. For these uncured patients, the mean and median survival time was 318 days (95% confidence interval [CI], 143-493) and 162 days (95% CI, 63-487), respectively. Table 1 represents the results of descriptive statistics of the subjects based on sex, the experience of pretransplantation relapse, type of HSCT, age (year), Hb (g/dl), MNCs (count), and BSA (m^2).

According to figure 1, for HL patients after HSCT and recurrence as the event of interest, the 1-, 3-, and 5-year survival rates were 88.9% (95% CI: 81.9 - 96.5), 83.4% (95% CI: 74.8 - 93.1), and 80.7% (95% CI: 71.1 - 91.6), respectively. It

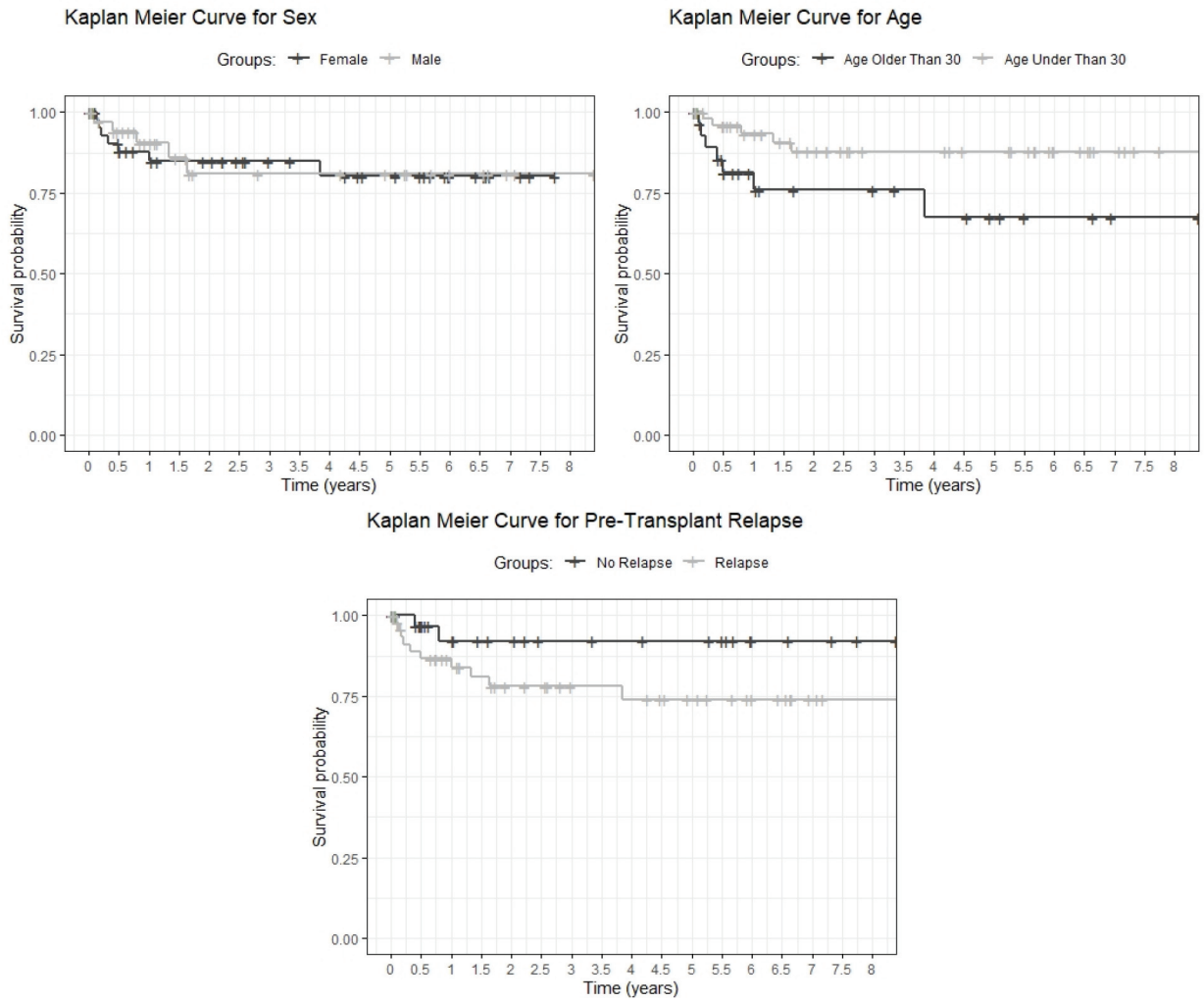

Figure 2. This figure shows the Kaplan-Meier survival curves of sex, age, and pretransplant relapse pertaining to the event of interest.

Table 3. hP cure rate for the risk factors in multiple analysis

Variables	Estimate	S.E.	*P*-value
η	1.530	0.57	10.007**
α	0.029	0.023	0.209
λ	1.881	0.044	<0.001**
Baseline	-0.184	0.664	0.780
BSA (m^2)	-0.149	0.037	<0.001**
Hb (g/dl)	0.076	0.022	0.008**
MNCs (count)	-0.126	0.019	<0.001**
Age			
over 30	-0.458	0.056	<0.001**
below 30***			
Sex			
Male	0.011	0.065	0.865
Female***			
Experience of relapse			
No	1.252	0.086	<0.001***
Yes***			

S.E.: Standard error; ** Significance at the 5% level; ***Reference category; η: Dispersion parameter of hP; α: Shape parameter of Weibull distribution; λ: Scale parameter of Weibull distribution; BSA: Body surface area; Hb: Hemoglobin; MNCs: Mononuclear cells; *Significance at the 10% level

is visible that a large proportion of the patients had not experienced the recurrence within approximately four years after HSCT. For estimation of the cure rate, hP distribution was used as discrete frailty in the next step. The aforementioned factors for patients with HL were examined via simple analysis. hb ($P = 0.008$), sex ($P = 0.019$), age ($P < 0.001$), MNCs ($P < 0.001$), BSA ($P < 0.001$), and experience of relapses ($P < 0.001$) were independently significant, which had a significant effect on the cure of HL patients following HSCT. However, the type of transplantation was not a significant factor ($P = 0.792$) on the cure of HL patients after HSCT, as shown in table 1.

Table 2 depicts the results obtained from simple analysis for each of the risk factors on the survival time through the application of the cure rate model with hP frailty distribution. As could be seen, the cure rate for the patients over 30 years old was 65.9%, while for those younger than 30, it was 87.3%. Cure rate decreased from 90.7% to 73.2% for the patients without any relapses in comparison with those who experienced at least one relapse. The cure rate was statistically affected by sex differences, with males having a slightly higher probability of cure than females, as shown in figure 2. Another point that warrants attention is that the type of transplantation had no significant effects on the cure of the patients. Finally, cure rates for the mean values of Hb, MNCs, and BSA were 80.8%, 80.4%, and 82.6%, respectively.

Table 3 illustrates the results of the multiple analysis. The significance of adjusted effects of Hb ($P = 0.008$), total of MNCs ($P < 0.001$), BSA ($P < 0.001$), age of over or below 30 years old ($P < 0.001$), and the experience of pre-transplantation relapse ($P < 0.001$) were obtained. Since $\eta > 1$, the overdispersion implied by the obtained data, which was probably the result of an increased number of cured patients, was estimated with hP distribution to get the best fit. Primarily, it is essential to note that sex did not have an adjusted significant effect on the multiple analysis ($P = 0.865$). Overall, by setting the values of Hb (9.34 g/deciliter), a total count of MNCs (5.99) and BSA (3.43 m^2) at their means, cure rates varied in multiple analysis setting. The cure rate for the subjects older than 30, with or without the experience of at least one relapse was 60.6% and 87.9%, respectively. The results concerning those younger than 30 changed and the patients who experienced the relapse had the cure rate of 74.1%, while the cure rate for those without this experience was 92.2%, as shown in table 4. Therefore, the lowest cure rate belonged to the patients older than 30 with the experience of at least one relapse before transplantation. On the

Table 4. hP cure rate when Hb, MNCs, and BSA were set to their means

Age	Experience of relapse	hP cure rate
over 30	Yes	0.606
	No	0.879
below 30	Yes	0.741
	No	0.922

BSA: Body surface area; Hb: Hemoglobin; MNCs: Mononuclear cells; hp: Hyper-Poisson distribution

other hand, the highest cure rate was obtained for those less than 30 years old who did not experience the relapse before transplantation.

Discussion

Even though numerous risk factors have been described for HL patients relapsing after first-line therapy, reliable risk factors are still needed for those undergoing HSCT. Once the recurrence of HL was regarded as the outcome, we found that the age of over 30, low Hb (g/dl), high MNCs (count), high BSA (m^2), and the experience of relapse before HSCT were factors of poor outcome.

The curable benefit of HSCT, followed by auto-HSCT in patients with refractory or relapsed HL, is supported by two primary studies in the literature. In the study by British National Lymphoma Investigation, the actuarial 3-year event-free survival has been found to be 53% and freedom from the treatment failure rate in the German Hodgkin Study Group (GHSG), reported together with the European Group for Blood and Marrow Transplantation, has been assumed 55%.[25,26] In Iran, the 3-year disease-free survival has been found to be 77% (SE 3.7%) for HL patients by studying stem cell transplantation with 20 years of experience.[13]

Group ages 20 to 34 years, which forms almost one-third of new diagnoses, are the most common ages in HL patients.[27] In our study, where about two-thirds of the subjects were below the age of 30, the analyses recognized the importance of age in the way that these patients had considerably higher cure rates. Studies have not mostly considered age as a significant factor in HL patients after HSCT, probably since most patients are relatively young at the time of transplantation and elderly patients are ineligible for transplantation.[20,28,29] A recent study by Talleur et al. demonstrated the significant improvement of outcome in 74 young patients with refractory or relapsed HL after auto-HSCT over time.[30] Pediatric patients have; however, 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.[31] By extending the follow-up time to 20 years, in contrast, the advanced age was reported as an unfortunate outcome of HL patients after HSCT in the study by Majhail et al.[32]

In 2019, the four-year disease-free survival for patients with relapsed or refractory HL after auto-HSCT as an established treatment was 65.3% based on the report by Iranian stem cell transplantation; however, the role of allogeneic HSCT (allo-HSCT) in relapsed or refractory HD has not yet been entirely determined.[13] Even though auto-HSCT is known as a standard treatment option for relapsed or refractory HL, allo-HSCT has its advantage: the usage of unaffected donor marrow cells, which avoids the risk of pervading tumor cells to relapse. Nevertheless, donor availability, age limitations, and higher treatment-related mortality have restricted a broader application and feasibility of allo-HSCT in HL.[33,34] A case-matched analysis was performed by Milpied et al., which concluded that there were no significant differences between transplantations.[35] The 4-year survival probability was 37 and 25 after auto-HSCT and allo-HSCT, respectively. This difference was mainly due to a higher transplant-related mortality rate in allo-SCT. In our analyses, auto-HSCT was not significantly better than allo-HSCT regarding the cure of the patients, perhaps because the patients with allo-HSCT comprised only 11% of the study population.

Anemia resulted from low Hb is one of the most prevalent hematological indicators of HL. In the retrospective analysis by GHSG, low Hb had been identified as one of the adverse prognostic factors along with ages older than 45 and advanced stage of HL for tumor control.[36,37] In addition, Hb was considered as one of the seven factors of the International Prognostic Score for advanced-stage HL patients.[38] These findings, aligned with our results, clarify the importance of Hb in patients with HL as they all emphasize the adverse effect of low Hb on the cure rate of HL patients. However, it is noteworthy that pregnancy could affect the Hb results by declining its value, which was not controlled in our study and should be considered in further studies.[39]

Several studies have evaluated the factor of sex on the survival of the HL patients whereas a few of them considered this factor after HSCT. In the study on head and neck lymphoma in an Iranian population, the difference between gender was significant in HL patients, where women had more survival time before HSCT.[40] However, after HSCT, sex was not a prognostic risk factor in the study by Josting et al., which regarded anemia as the only risk factor.[14] Although we found that males with relapsed or refractory HL after HSCT had gained a slightly better cure rate than females, the difference between the genders was not statistically significant when all the causes of recurrence were considered in this study. Several factors, including study design, sample size, and genetic and environmental discrepancies, may be responsible for these differences.

In the post-transplant setting, MNCs has been shown to be effective. MNCs are one of the characteristics of classical HL and LPHL (lymphocyte-predominant Hodgkin lymphoma). Several HL cell lines-associated studies have indicated that the mononuclear Hodgkin cells give rise to the RS cancerous cells. By this proliferation, the cure fraction of patients declines accordingly.[41]

BSA of patients declines by losing weight. In the early stages of the disease, B symptoms (systemic symptoms of fever, night sweats, and weight loss) are associated with unfavorable outcomes. However, Brockelman et al. recently developed a prognostic score for PFS by conducting a multivariable analysis for patients with refractory or relapsed HL undergoing auto-HSCT. In this international project, B symptoms were evaluated, yet its significance was not confirmed.[42] On the other side of the spectrum, obesity can alter immune function, which is commonly measured through the body mass index (BMI) and increase the risk of HL.[43] After auto-HSCT; however, a low body mass index was correlated with poor survival in the study by Le Blanc et al.[44] Despite these facts, studies that have evaluated BSA's role instead of BMI on the cure of HL had not been considered yet. BSA values are commonly used in medicine, particularly to calculate drug dosages. In our study, increased values of BSA led to the declination of a cure fraction of HL patients. The low number of patients may explain this contrast. The primary limitation of our study was the low number of HL patients who underwent HSCT. This limitation might be due to the rareness of the disease and a high initial cure rate of first-line therapy. It is also worth mentioning that the data gathered from a single institution, which included missing or incorrectly recorded data of certain clinical and biological variables, made valuable information useless. However, our study strengthened the status of HSCT in refractory or relapsed HL patients, while adding valuable information about risk factors using a cure rate model with a flexible hP distribution for frailty variable to account for heterogeneity among the patients.

Conclusion

This paper proposed a model for accommodating long-term survival data obtained from a discrete frailty model by assuming hP distribution. Age, the experience of pretransplantation relapse, Hb, MNCs, and BSA were found to be associated with the cure of HL patients after HSCT when the event of interest was a recurrence. Based on this study, post-transplant consolidation therapies and the following risk-adapted approaches for treating HL patients after HSCT

could be considered.

Acknowledgment

This study was supported by the School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Furthermore, we would like to acknowledge the staff of the department of bone marrow transplantation of Taleghani Hospital for their contribution during the data gathering.

Conflict of Interest

None declared.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA , Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492.
2. Zhou L, Deng Y, Li N, Zheng Y, Tian T, Zhai Z, et al. Global, regional, and national burden of Hodgkin lymphoma from 1990 to 2017: estimates from the 2017 Global Burden of Disease study. *J Hematol Oncol.* 2019;12(1):107. doi: 10.1186/s13045-019-0799-1.
3. World Health Organization., IARC monographs on the evaluation of carcinogenic risks to humans: Some Traditional Herbal Medicines, Some Mycotoxins, Naphthaleneand Styrene. Lyon; 2002, Vol 82. 978-92-832-1582-0.
4. Engert A, Pl¸tschow A, Eich HT, Lohri A, Dörken B, Borchmann P, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med.* 2010;363(7):640-52. doi: 10.1056/NEJMoa 1000067.
5. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1736-88. doi: 10.1016/S0140-6736(18)32203-7. Erratum in: *Lancet.* 2019;393(10190):e44. Erratum in: *Lancet.* 2018;392(10160):2170.
6. von Tresckow B , Moskowitz CH. Treatment of relapsed and refractory Hodgkin lymphoma. *Semin Hematol.* 2016;53(3):180-5. doi:10.1053/j.seminhematol.2016.05.010.
7. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet.* 1993;341(8852):1051-4. doi: 10.1016/0140-6736(93)92411-l.
8. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet.* 2002;359(9323):2065-71. doi: 10.1016/S0140-6736(02)08938-9.
9. Josting A, Reiser M, Rueffer U, Salzberger B, Diehl V , Engert A. Treatment of primary progressive Hodgkin's and aggressive non-Hodgkin's lymphoma: is there a chance for cure? *J Clin Oncol.* 2000;18(2):332-9. doi:10.1200/jco.2000.18.2.332.
10. Reece DE, Connors JM, Spinelli JJ, Barnett MJ, Fairey RN, Klingemann HG, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide +/- cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood.* 1994;83(5):1193-9.
11. Sayadi L, Jafaraghaee F, Jeddian A, Atrian MK, Akbari A , Tootoonchian F. Views of patients undergo hematopoietic stem cell transplantation on their basic needs. *Int J Hematol Oncol Stem Cell Res.* 2013;7(2):23-9.
12. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA.* 2010;303(16):1617-24. doi: 10.1001/jama.2010.491.
13. Ghavamzadeh A, Alimoghaddam K, Ghaffari F, Derakhshandeh R, Jalali A , Jahani M. Twenty years of experience on stem cell transplantation in iran. *Iran Red Crescent Med J.* 2013;15(2):93-100. doi:10.5812/ircmj.1915.
14. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. *J Clin Oncol.* 2002;20(1):221-30. doi: 10.1200/JCO.2002.20.1.221.
15. Sureda A, Constans M, Iriondo A, Arranz R, Caballero MD, Vidal MJ, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. *Ann Oncol.* 2005;16(4):625-33. doi: 10.1093/annonc/mdi119.
16. Satwani P, Ahn KW, Carreras J, Abdel-Azim H, Cairo MS, Cashen A, et al. A prognostic model predicting autologous transplantation outcomes in children, adolescents and young adults with Hodgkin lymphoma. *Bone Marrow Transplant.* 2015;50(11):1416-23. doi: 10.1038/bmt.2015.177.
17. Perdoná GC , Louzada-Neto F. A general hazard model for lifetime data in the presence of cure rate. *J Appl Stat.* 2011;38(7):1395-405. doi:10.1080/02664763.2010.505948.
18. Barriga GD, Cancho VG, Garibay DV, Cordeiro GM,

Ortega EM. A new survival model with surviving fraction: An application to colorectal cancer data. *Stat Methods Med Res.* 2019;28(9):2665-80. doi:10.1177/0962280218786053.
19. de Souza D, Cancho VG, Rodrigues J , Balakrishnan N. Bayesian cure rate models induced by frailty in survival analysis. *Stat Methods Med Res.* 2017;26(5):2011-28. doi:10.1177/0962280217708671.
20. Brice P, Bouabdallah R, Moreau P, Divine M, AndrÈ M, Aoudjane M, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. *Bone Marrow Transplant.* 1997;20(1):21-6. doi: 10.1038/sj.bmt.1700838.
21. Devetten MP, Hari PN, Carreras J, Logan BR, van Besien K, Bredeson CN, et al. Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2009;15(1):109-17. doi: 10.1016/j.bbmt.2008.11.011.
22. Townsend W, Leong S, Hoskin P, Diez P, Patrick P, Linch D, et al. Treatment of classical Hodgkin lymphoma in young adults aged 18-30 years with a modified paediatric Hodgkin lymphoma protocol. Results of a multicentre phase II clinical trial (CRUK/08/012). *Br J Haematol.* 2020;189(1):128-32. doi: 10.1111/bjh.16296.
23. Cancho VG, Barriga G, Leão J , Saulo H. Survival model induced by discrete frailty for modeling of lifetime data with long-term survivors and change-point. *Commun Stat Theory Methods.* 2019:1-12. doi:10.1080/03610926.2019.1648826.
24. Bardwell GE , Crow EL. A two-parameter family of hyper-poisson distributions. *J Am Stat Assoc.* 1964;59(305):133-41. doi:10.1080/01621459.1964.10480706.
25. Josting A, Rudolph C, Mapara M, Glossmann JP, Sieniawski M, Sieber M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group (GHSG). *Ann Oncol.* 2005;16(1):116-23. doi: 10.1093/annonc/mdi003. Erratum in: *Ann Oncol.* 2008;19(8):1515. Sienawski, M [corrected to Sieniawski, M]. Erratum in: *Ann Oncol.* 2008;19(8):1515.
26. Kwan A, Chadwick N , Hancock B. Improving survival of patients with Hodgkin lymphoma over 4 decades: Experience of the British National Lymphoma Investigation (BNLI) With 6834 patients. *Clin Lymphoma Myeloma Leuk.* 2017;17(2):108-19. doi:10.1016/j.clml.2016.11.004.
27. Shanbhag S , Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. *CA Cancer J Clin.* 2018;68(2):116-32. doi:10.3322/caac.21438.
28. Bierman PJ, Bagin RG, Jagannath S, Vose JM, Spitzer G, Kessinger A, et al. High dose chemotherapy followed by autologous hematopoietic rescue in Hodgkin's disease: long-term follow-up in 128 patients. *Ann Oncol.* 1993;4(9):767-73. doi: 10.1093/oxfordjournals.annonc.a058662.
29. Horning SJ, Chao NJ, Negrin RS, Hoppe RT, Long GD, Hu WW, et al. High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: analysis of the Stanford University results and prognostic indices. *Blood.* 1997;89(3):801-13.
30. Talleur AC, Flerlage JE, Shook DR, Chilsen AM, Hudson MM, Cheng C, et al. Autologous hematopoietic cell transplantation for the treatment of relapsed/refractory pediatric, adolescent, and young adult Hodgkin lymphoma: a single institutional experience. *Bone Marrow Transplant.* 2020;55(7):1357-66. doi: 10.1038/s41409-020-0879-4.
31. Williams CD, Goldstone AH, Pearce R, Green S, Armitage JO, Carella A, et al. Autologous bone marrow transplantation for pediatric Hodgkin's disease: a case-matched comparison with adult patients by the European Bone Marrow Transplant Group Lymphoma Registry. *J Clin Oncol.* 1993;11(11):2243-9. doi: 10.1200/JCO.1993.11.11.2243.
32. Majhail NS, Weisdorf DJ, Defor TE, Miller JS, McGlave PB, Slungaard A, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biol Blood Marrow Transplant.* 2006;12(10):1065-72. doi: 10.1016/j.bbmt.2006.06.006.
33. Anderson JE, Litzow MR, Appelbaum FR, Schoch G, Fisher LD, Buckner CD, et al. Allogeneic, syngeneic, and autologous marrow transplantation for Hodgkin's disease: the 21-year Seattle experience. *J Clin Oncol.* 1993;11(12):2342-50. doi: 10.1200/JCO.1993.11.12.2342.
34. Jones RJ, Piantadosi S, Mann RB, Ambinder RF, Seifter EJ, Vriesendorp HM, et al. High-dose cytotoxic therapy and bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol.* 1990;8(3):527-37. doi: 10.1200/JCO.1990.8.3.527.
35. Milpied N, Fielding AK, Pearce RM, Ernst P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. European Group for Blood and Bone Marrow Transplantation. *J Clin Oncol.* 1996;14(4):1291-6. doi:10.1200/jco.1996.14.4.1291.
36. Argiris A, Seropian S , Cooper DL. High-dose BEAM chemotherapy with autologous peripheral blood progenitor-cell transplantation for unselected patients with primary refractory or relapsed Hodgkin's disease. *Ann Oncol.* 2000;11(6):665-72. doi:10.1023/a:1008396525292.
37. FermÈ C, Mounier N, DivinÈ M, Brice P, Stamatoullas

A, Reman O, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. *J Clin Oncol*. 2002;20(2):467-75. doi: 10.1200/JCO.2002.20.2.467.
38. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med.* 1998;339(21):1506-14. doi:10.1056/nejm199811193392104.
39. Moghaddam Tabrizi F, Barjasteh S. Maternal hemoglobin levels during pregnancy and their association with birth weight of neonates. *Iran J Ped Hematol Oncol.* 2015;5(4):211-7.
40. Shamloo N, Ghannadan A, Jafari M, Ahmadi S, Mortazavi H , Baharvand M. Head and neck lymphoma in an Iranian population. *Iran J Otorhinolaryngol.* 2017;29(94):261-7. doi:10.22038/IJORL.2017.21392.1715.
41. Newcom SR, Kadin ME, Phillips C. L-428 Reed-Sternberg cells and mononuclear Hodgkin's cells arise from a single cloned mononuclear cell. *Int J Cell Cloning.* 1988;6(6):417-31. doi:10.1002/stem.5530060606.
42. Bröckelmann PJ, Müller H, Casasnovas O, Hutchings M, von Tresckow B, J¸rgens M, et al. Risk factors and a prognostic score for survival after autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma. *Ann Oncol.* 2017;28(6):1352-8. doi: 10.1093/annonc/mdx072.
43. Strongman H, Brown A, Smeeth L , Bhaskaran K. Body mass index and Hodgkin's lymphoma: UK population-based cohort study of 5.8 million individuals. *Br J Cancer.* 2019;120(7):768-70. doi:10.1038/s41416-019-0401-1.
44. Le Blanc K, RingdÈn O, Remberger M. A low body mass index is correlated with poor survival after allogeneic stem cell transplantation. *Haematologica.* 2003;88(9):1044-52.