Original Article

# A Cure Rate Model with Discrete Frailty on Hodgkin Lymphoma Patients after Diagnosis

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## Abstract

**Introduction:** Hodgkin lymphoma (HL) is an uncommon cancer of lymphocytes, characterized by cancerous Reed-Sternberg cells in an inflammatory background. HL is an exceptionally curable disease with combination chemotherapy, radiotherapy, or combined modality treatment. This analysis aimed to identify significant prognostic factors on the cure rate.

**Materials and Methods:** The medical records of 110 patients hospitalized from 2007 up to 2014 with 18 months follow-up was retrospectively reviewed in Taleghani hospital of Tehran, Iran. The survival time was set as the time interval between diagnosis and a patient's death from HL. Also, if the cure rate was present in survival, data encompasses zero frailty. Thus, using hyper-Poisson (hP) distribution as discrete frailty, the unobserved heterogeneity and random effects were accounted for.

**Results:** The estimated cure fraction was 81.2%, which was obtained after 2717 days (7.4 years). In noncured cases, the mean survival time was 1535 days (4.2 years). Also, the five and ten-year survival rates were 0.91 and 0.80, respectively. After diagnosis, results revealed that patients with age $\geq$ 45, hemoglobin $\leq$ 12, WBC $\geq$ 15000, and BMI $\geq$ 30 were associated with poor outcome by using simple analysis. More importantly, there is no significant difference between males and females in the cure of HL patients.

**Conclusion:** As expected, the study indicated that a high proportion of HL patients got cured. A cure rate model with discrete frailty utilization provided a suitable way to account for heterogeneity among HL patients.

**Keywords**: Hodgkin's Lymphoma, Survival Analysis, Cure Rate Model, Discrete Frailty

## 1. Introduction

Hodgkin lymphoma (HL), initially called Hodgkin's disease, is a rare monoclonal lymphoid neoplasm with high cure rates. HL is divided into two distinct categories by biological studies: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). Classical Hodgkin lymphoma comprises the majority of the subtypes (accounting for approximately 95% of all HL) [1]. The age-adjusted death rate was 0.3 per 100,000 men and women per year based on 2014–2018 deaths statistics. In

2020, it is estimated that there are 8,480 new cases of Hodgkin lymphoma, and 970 people would die from the disease [2].
Nevertheless, the cure rate is high in patients with HL. Chemotherapy and radiation therapy are the two main treatment methods, and if both methods are used simultaneously, more desirable results are to be achieved [3]. This progress in achieving a high cure rate is mainly due to

the development of clinical and treatment methods such as multi-agent chemotherapy and radiotherapy improvements [4]. HL represents a heterogeneous group of malignant lymphoid neoplasms, accounting for a significant proportion of cancers occurring in kids, teenagers, and young adults, which has made the disease with an age distribution with two modes and a tip incidence in the 15–34-year age group and a second in the over 60-year-old group [5]. Moreover, HL ranked as the 21st most common cancer through accounting for 1% of all new cases (approximately 1140 cases in 2018) in Iran [6].

HL has become a standard to study thriving radiotherapy and chemotherapy's long-term effects as development in diagnosis and the generally young age of patients afflicted. Most patients' treatment is chemotherapy (usually 2 to 4 cycles), followed by radiation to the disease's initial site. ABVD as standard chemotherapy treatment followed by involved-field irradiation is considered the standard care for HL, providing an excellent balance of efficiency and toxicity. More potent combinations, such as the BEACOPP regimen, are being investigated, usually in patients with unfavorable early-stage HL [7, 8]. Still, radiation therapy plays a chief role in the treatment of early-stage HL. Currently, most patients with HL are managed with combined modality programs in which radiation therapy is given as stabilization method after chemotherapy [7, 9].

As a member of the population under study, each individual met the event of interest in survival analysis studies. In other words, one of the main assumptions in survival analysis was the homogeneity among individuals [10]. Nevertheless, the presence of a proportion of entirely cured patients of a distinct disease who did not suffer any loss, death, or recurrence was not neglected as the rapid progression in the biomedical and drug industry. These people were considered cured patients [11]. If the follow-up time was long enough, there were cured individuals in the dataset. Therefore, the population under study were considered a composite of cured patients and susceptible, and as such, the application of cure rate models was more suitable than the classical survival models [12]. Though covariates may explain heterogeneity, unobserved heterogeneity could be observed when significant covariates have not been included in the study. Frailty was defined as a random, multiplicative factor applying to the hazard function to account for unobserved heterogeneity among individuals [13]. The hyper-Poisson distribution (hP) is a flexible distribution from the family of discrete distributions since it can be over-dispersed or under dispersed depending on the value of the dispersion parameter [14].

## 2. Materials and Methods

The data of 110 patients were extracted for this analysis after deleting subjects with incomplete data and missing observation times. For initial examination, patients were referred to Taleghani Hospital (affiliated to the Shahid Beheshti University of Medical Sciences), Tehran, Iran, and then treated by first-line therapy at the bone marrow transplantation department, from 2007 to the end of 2014, with a follow-up of 18 months. Follow-up time was considered to determine patients' survival status who were contacted by telephone, and their survival conditions were recorded from March 2015 to August 2016.

The Patients’ information data in this study included sex, white cell counts (WBC), hemoglobin (Hb), body mass index (BMI), age at the time of diagnosis, survival status, and survival time by days. The event variable was defined as death from the disease; therefore, the survival time was calculated by the difference between the time of diagnosis and the death of the patient.

In the Kaplan-Meier plot, a long plateau with a reasonable follow-up time justifies the cure rate models' usage. Also, the frailty

approach serves as an appropriate statistical modeling method to explain the heterogeneity of the data which was caused by unobserved covariates. Each patient had its frailty, and patients with higher frailty were more prone to having the event earlier [15]. HL patients cured by first-line therapy were considered individuals who did not experience the event of interest. In other words, the event of interest did not happen even after a long period of observation. These non-susceptible individuals, called cured patients, encompass zero frailty [13, 16]. In this situation, models induced by frailty with a non-negative and continuous distribution were not considered as proper anymore. Hence, discrete frailty was essential to model the cured patients accurately. Hyper-Poisson distribution (hP) was introduced for the first time by Bardwell and Crow in 1964 for modeling the count data. The important characteristic of hP is the flexibility of this distribution, which indicates that the Poisson regression model's equidispersion assumption is not a limitation anymore [14]. Generally, the Weibull model can be an adequate alternative for baseline distribution with $\alpha$ and $\lambda$ as shape and scale parameters, respectively [17]. The frequency for categorical variables was used to summarize demographic and prognostic variables in the population's study. Then, simple analysis for the effect of variables on the cure fraction was evaluated. This study was conducted after approval of the Ethics Committee of Shahid Beheshti University of Medical Science (code: IR.SBMU.RETECH.REC.1396.966). All statistical analyses were performed by R programming language version 4.0.1 (packages: dplyr, ggplot2, survival, stats), and the p-value $< 0.05$ were considered as the level of statistical significance.

## 3. Results

Of 110 individuals who were diagnosed with Hodgkin lymphoma, 47.2% were men, and 52.8% were women. At the time of diagnosis, 8.1% of patients were greater than or equal to 45 years old, and 91.9% were less than 45 years old. While 94.5% of HL patients had WBC more than 15000/mm$^3$, 5.5% had less than 15000/mm$^3$. Results of descriptive statistics of subjects based on sex, age, WBC, Hb, and BMI were presented in Table 1.

After diagnosis, 11% of patients died from the disease. The mean survival time for these uncured patients was 1535 days (95% confidence interval [CI], 699-2371).

**Table 1.** Descriptive Statistics of variables

| Variables | Number of patients | Percentage |
|---|---|---|
| **Age** | | |
| Age $\geq$ 45 | 9 | 8.1% |
| Age $<$ 45 | 101 | 91.9% |
| **Sex** | | |
| Male | 52 | 47.2% |
| Female | 58 | 52.8% |
| **Obesity** | | |
| BMI $\geq$ 30 | 23 | 20.9% |
| BMI $<$ 30 | 87 | 79.1% |
| **WBC (mm$^3$)** | | |
| WBC $\geq$ 15000 | 6 | 5.5% |
| WBC $<$ 15000 | 104 | 94.5% |
| **Anemia (g/dl)** | | |
| Hemoglobin $\leq$ 12 | 106 | 96.4% |
| Hemoglobin $>$ 12 | 4 | 3.6% |

The 5-year and 10-year survival rates were 91.5% (95% CI: 85.5 - 97.9), 80.1% (95% CI: 70.0 - 91.8), respectively. From the Kaplan-Meier plot in Figure 1, a large proportion of patients had not experienced the death within 2717 days (approximately eight years) after diagnosis.

In the next step, hP distribution was used as discrete frailty to estimate the cure rate. The estimated cure fraction of the model by the usage of hP was 81.2%. The factors, as mentioned earlier, had been examined independently. Hb (p-value: 0.041), age (p-value < 0.001), BMI (p-value < 0.001), and WBC (p-value: 0.007) were independently significant which means that except for the sex (p-value: 0.197), all considered variables had a significant effect on the healing of HL patients after diagnosis.

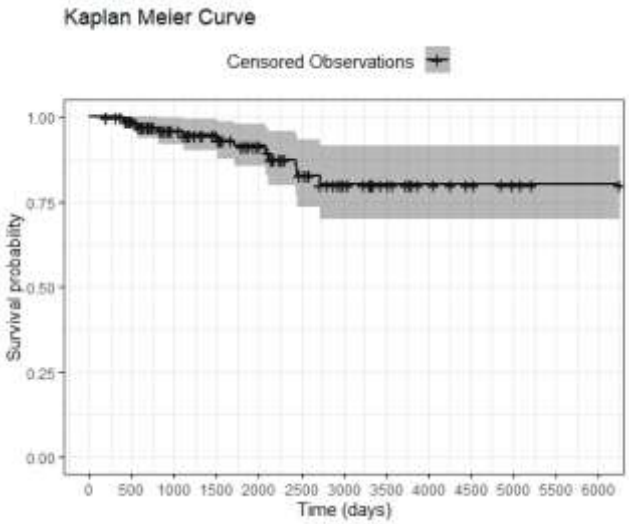
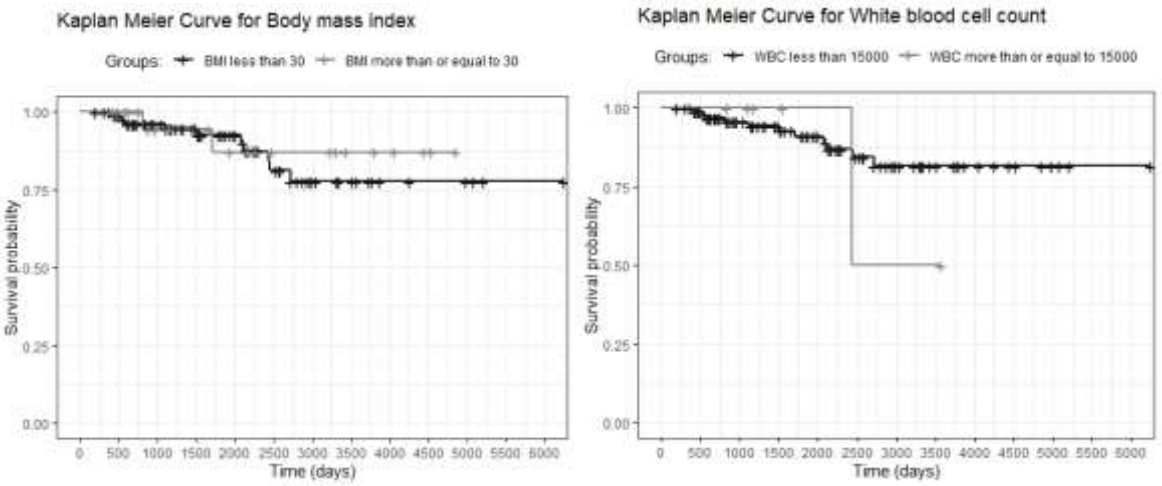



Figure 1. Kaplan-Meier curve for the population of the study

Also, the Kaplan-Meier curves for each variable of the study are presented in Figure 2.



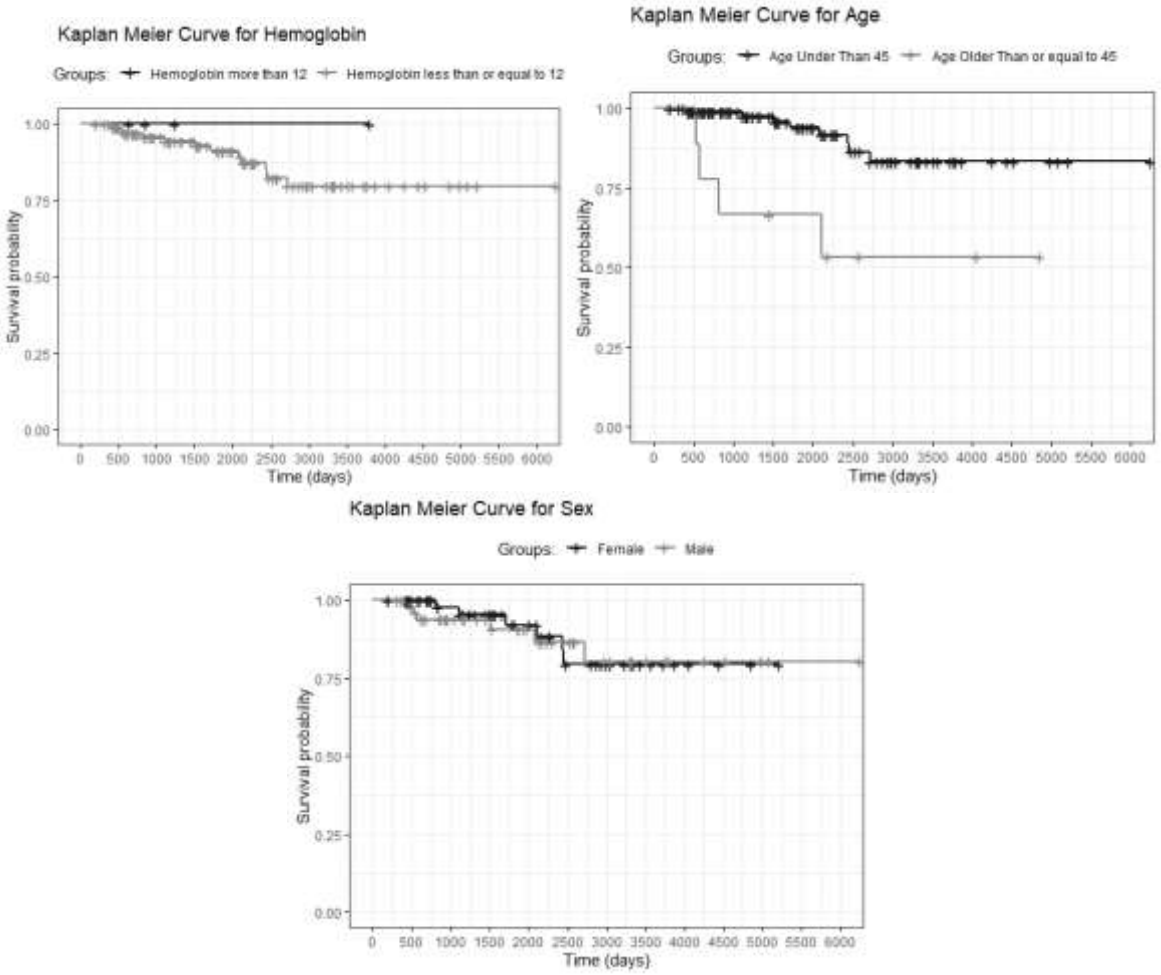



**Figure 2.** Kaplan-Meier curves for variables of the study

The simple analysis results are presented in table 2 via using the maximum likelihood method for each level of the risk factors. As was shown, the cure rate for patients more than or equal to 45 years old was 40.9%, while for patients younger than 45, it was 84.5%. Cure rate falls from 78.7% to 71.4% for patients with WBC less than 15000/mm$^3$ compared to patients who had WBC more than 15000/mm$^3$. The hP cure rate for patients with less than or equal to 12 (g/dL) of Hb was 77.9%. In other words, patients with a low level of Hb had less cure rate. It is crucial to note that sex had no significant effect on the cure of patients. Finally, the cure rate for patients with a BMI of less than 30 was 84.5%, while for patients with more than or equal to 30 was 76.8%.

**Table 2.** hP Cure Rate for Risk Factors in Simple Analysis

| **Variables** | **hP Cure rate** | **Estimate (S.E)**$^{***}$ | **P-Value** |
|---|---|---|---|
| **Age** | | | <0.001$^{*}$ |
| Age $\geq$ 45 | 0.409 | 1.38 (0.04) | |
| Age $<$ 45$^{**}$ | 0.845 | - | |
| **Sex** | | | 0.197 |
| Male | - | 0.06 (0.48) | |
| Female$^{**}$ | - | - | |

| | | | |
|---|---|---|---|
| **WBC** | | | 0.007* |
| WBC ≥ 15000 | 0.714 | 0.38 (0.14) | |
| WBC < 15000** | 0.787 | - | |
| **Hemoglobin** | | | 0.041* |
| Hemoglobin ≤ 12 | 0.779 | 5.46 (2.68) | |
| Hemoglobin > 12** | 0.999 | - | |
| **BMI** | | | <0.001* |
| BMI ≥ 30 | 0.768 | 0.49 (0.08) | |
| BMI < 30** | 0.845 | - | |

*Significance at the 5% level **Reference Category ***Standard Error

## 4. Discussion

With the advancement of treatment methods like chemotherapy or radiotherapy in recent years, it is reasonable to expect patients to gain high cure rates. When the death from HL was considered as the outcome of the study, age greater than or equal to 45 years old, low Hb (g/dL), high level of WBC, and BMI were factors of poor outcome, independently. In 2018, Brockelmann et al. studied the survival of HL patients to a great extent; results of many randomized and controlled trials, meta-analyses, prospective or retrospective studies were evaluated [18]. In the end, the five-year survival of patients with Hodgkin lymphoma was obtained 95%. In Iran, the probability of survival for HL patients demonstrated that the five- and 10-year-survival rates were 65 and 61.3 percent, respectively [19]. In 2015, through the analysis of long-term survival and cure fractions of Hodgkin's Disease patients, Bouliotis and Bessell obtained the cure fraction 75% for the 1993-2002 cohort [20]. The International Prognostic Score (IPS-7) serves as one of Hodgkin's lymphoma's most broadly risk stratification index [21]. Biologically, the factors included in the prognostic score are reasonable and practical. Age ≥ 45 years and male sex independently associated with a more unsatisfactory outcome of Hodgkin's lymphoma accompanied by hemoglobin < 10.5 g/dL, WBC count ≥ 15000/mm$^3$, lymphocyte count < 600/mm$^3$, albumin < 40 g/dL. According to the number of risk factors, patients who were in the analysis and were treated between 1983 and 1992 represent different freedom from disease progression rates. Patients with five or more risk factors were compared with patients with no risk factor. The difference was significant in a way that the former group had a freedom from disease progression rate of 42%, and the latter group had 84%. However, due to the enhanced outcomes with current therapy, recent studies suggest that the discriminating impact of the IPS-7 has reduced [22]. In the present study, age was significant in the cure fraction of the patients. Patients older than 45 had less hP cure rate than patients with less than 45. Likewise, Hasenclever et al. also demonstrated that age was a significant factor in the survival of the HL patients so that patients more than 45 years-old had less survival probability [23]. Due to improved outcomes with contemporary treatment methods, Diefenbach et al. tried to replace IPS-7 with IPS-3, which finally concluded that age, Hb, and stage are significant factors on the HL patients [22]. Although being male was considered as a significant factor in survival by IPS-7, in this study, sex had no significant effect on the cure of patients at 5% level of significance. In one 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 [24].

Based on the disease's high stage, absolute lymphocyte count, male gender, and age ≥ 45, another defined risk group has been confirmed [25]. However, the male gender was not significant in the study by Straus et al [26]. HL is a type of cancer that affects specialized white blood cells called lymphocytes. WBC was a significant factor in the present study when WBC ≥ 15000/mm$^3$ aligned with IPS-7 [21]. According to the study by Hohaus et al., anemia is present at diagnosis in approximately 40% of patients with HL [27]. Anemia was defined as Hb level <12 g/dl in this study and was an independently significant factor in patients' cure. These findings, aligned with the present study, clarify the importance of Hb in patients with HL as they all emphasized the adverse effect of low Hb on the cure rate. However, it is essential to note that pregnancy can affect the Hb results, which was not controlled in our study and should be considered in further studies [28]. Obesity can modify the immune function and thus may increase the risk of Hodgkin's lymphoma (HL). Renehan et al., by studying obesity and Hodgkin lymphoma's risk, suggests a positive association between body mass index (BMI) and HL [29]. Also, according to the study by Keegan et al., in young adult women, the higher body mass index levels were associated with increased HL risk compared to older women. [30]. The primary encountering limitation of this study was a low number of HL patients due to the rareness of the disease; hence, research with more sample size is suggested for further studies.

## 5. Conclusion

This paper proposed a model for accommodating long-term survival data obtained from a discrete frailty model by assuming hyper-Poisson distribution. Age ≥ 45, hemoglobin ≤ 12, WBC ≥ 15000, and BMI ≥ 30 were associated with the cure of HL patients after diagnosis when the event of interest was a death.

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## Conflict of interest

The authors declare no conflict of interest.

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