



Bayesian Parametric Survival Analysis of Patients With Non-Hodgkin's Lymphoma in Yazd, Iran, During 2009-2019

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Abstract

Background and aims: Non-Hodgkin's lymphoma (NHL) is one of two main types of lymphoma. This present study aimed to investigate the survival rate in patients with NHL.

Methods: This analytical survival-type study examined 372 patients with NHL referred to Shahid Sadoughi Hospital in Yazd in 2009-2019. The data were extracted from patients' files. STATA/17 software, the Kaplan-Meier method, and Bayesian parametric survival analysis were used for data analysis.

Results: The overall survival rate and the mean overall survival time were 65% and 129±17.94 months, respectively. According to the Kaplan-Meier method, the survival rates of 1, 2, 3, 5, and 10 years were 86%, 80%, 76%, 69.5%, and 52%. The results revealed that men, people over 70 years old, patients with the NHL.T-cell subtype, patients with involvement in the chest, inguinal, and abdominal-pelvic regions, and patients in stage III or IV of the disease had a shorter survival time. In addition, survival time was shorter in patients with disease recurrence at the primary site. The variables of gender (hazard ratio [HR]=0.65; 95% confidence interval [CI]: 0.44–0.93), type of treatment (HR=3.43; 95% CI: 1.58–6.16), stage of disease (HR=2.87; 95% CI: 2.09–3.57), and involvement site (HR=1.45; 95% CI: 1.03–1.99) had a significant effect on survival time using the Bayesian parametric regression model.

Conclusion: If patients are identified at an early stage, they have the best chance of survival. In chronic lymphocytic leukemia (CLL) patients, the best survival is achieved without treatment. At the same time, in other types of cancer, chemotherapy offers the best survival.

Keywords: Bayesian parametric survival analysis, Non-Hodgkin's lymphoma, Yazd

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Introduction

Lymphomas can affect each of the organs of the body. It appears to have a wide range of symptoms. Lymphomas are divided into Hodgkin and non-Hodgkin categories. Non-Hodgkin's lymphomas (NHL) are a diverse group of blood cancers that are notoriously unpredictable and more likely to spread to locations outside the lymph nodes compared to Hodgkin's lymphomas.¹ NHL is one of the most common blood cancers. It is the 8th most common cancer in men and the 11th most common cancer in women.²

NHL has many subtypes, ranging from slow-growing to highly aggressive cancers.³ The NHL includes 2.8% of all new cancer diagnoses in the world.⁴ This disease is the seventh most common cancer and the sixth cause of cancer-related death in the United States.⁵ The findings indicate a decreasing trend in mortality and disability-adjusted life years caused by NHL worldwide from 1990 to 2019.⁶ However, the NHL remains a fundamental challenge at the global level. According to the World

Cancer Statistics 2018, the burden of NHL has increased in many geographic regions and reached 509 590 cases and 248 724 deaths in 2018.⁴ A meta-analysis study showed that the incidence of NHL in Iran is lower compared to other countries.²

According to the World Health Organization classification, NHL is classified into the B-cell and T-cell categories.⁷ About 95% of cases of this disease are related to the B-cell subtype, and the remaining 5% are related to the T-cell subtype.⁸ Diffuse large B-cell lymphoma, chronic lymphocytic leukemia (CLL), small lymphocytic leukemia, and follicular lymphoma are types of B-cell subgroup cancers.⁵

Due to the limited understanding of NHL creation, the process is reminiscent of a complex biological process involving multiple genetic factors and immune system disturbances.⁹ Primary and inherited immunodeficiencies, autoimmune disorders such as lupus, and infections such as the human immunodeficiency virus are among the risk factors for NHL.¹⁰ NHL prognosis is also linked to tumor

attributes (cancer type and stage) and patient attributes (age, gender, ethnicity, and socioeconomic status).¹¹

There are different approaches for treatment, including chemotherapy, radiotherapy, bone grafting, and the like, according to the characteristics of each type of conflict, such as molecular characteristics, clinical stage, location of the damaged tissue, and the like.¹² Fortunately, the survival rate has improved in recent years with the evolution of NHL therapeutic management, advances in treatment methods, and the use of targeted therapies and immunotherapy^{5,13,14} (e.g., adding CD20 to standard chemotherapy).¹³

Understanding the survival trend of NHL and its prognostic factors can help in its prevention and clinical treatment. In addition, determining the survival rate is an essential criterion for health planning and patient care programs. Considering that cancer epidemiology studies in Iran regarding NHL are limited, the present study was conducted to investigate the survival rate and related factors in patients with NHL using Bayesian refined models.

Materials and Methods

Study Design

The present survival analysis study examined the record files of all patients with NHL referred to Shahid Sadoughi Hospital in Yazd in 2009-19. By placing the values of $R^2=0.8$, $\beta=0.2$, and $P=0.8$,¹⁵ 372 patients diagnosed with NHL cancer by a doctor were selected and hospitalized in the Oncology and Hematology Department of Shahid Sadoughi Hospital of Yazd during 2009-2019.

Data Collection

This study extracted data from the medical files and recorded them in the checklist. The patient's survival was followed up through phone calls. Survival time was considered from the time of diagnosis to the time of death. Patients who were alive at the end of the study or had died of causes other than NHL were considered censored. Basic information included gender, age, disease subtype (B-cell, T-cell, Chronic lymphocytic leukemia (CLL), and Hairy cell leukemia [HCL]), site of involvement (head and neck, axillary, inguinal, abdominal-pelvic, chest, digestive system, and bone marrow), and stage of disease. The other basic data were the type of treatment (chemotherapy, chemotherapy-radiotherapy, chemotherapy-bone marrow transplant, chemotherapy-radiotherapy-bone marrow transplant, without treatment, and under follow-up), relapse status, and relapse site.

Data Analysis

The Bayesian parametric survival model is constructed in two separate parts. The first is the underlying survival time distribution, and the second is the distribution parameter obtained through a function of the input data. In addition, a set of prior coefficients estimated during the training phase is used. The most important probability

distributions for survival time are the exponential and Weibull distributions. The sampling method is random walk Metropolis-Hastings. Different likelihood models and prior distributions can be utilized in this method. A normal prior distribution was employed in this study.

This study applied the Kaplan-Meier method and log-rank test for data analysis. To investigate factors related to patients' survival, variables with a significance value of less than 0.2 in the univariate test (log-rank) and the literature review were entered into the model.¹⁶ The parametric survival regression model (Weibull, log-normal, and logistic) was used to model survival data. According to the Paolucci et al model, Bayesian parametric survival models perform well in advanced models, requiring less hyperparameter tuning and achieving higher efficiency.¹⁷ Therefore, this model was employed in the present study. First, all three Bayesian parametric survival models were fitted to the data, and the model with the lowest DIC criterion was selected. STATA software (version 17) was utilized for data analysis.

Results

In the present study, 238 (64%) patients were male, and 134 (36%) were female. The mean age was 84.71 years, ranging from 14 to 91 years. The results demonstrated that 218 people (58.6%) had B-cell NHL, 23 people (6.2%) had T-cell, 116 people (31.2%) had CLL, and 15 people (4%) had HCL. The most common histological subtype of NHL is diffuse large B-cell lymphoma (38.7%). Moreover, most patients (29%) were in stage III, and most people (79%) only used chemotherapy. The results showed that 35, 35, and 5 patients had recurrence in the primary location, in other locations, and in both locations, respectively (Table 1). According to the collected data, 176 people (3.47%) had lymphoma in the bone marrow (Table 2).

The findings revealed that 130 people (34.9%) died due to lymphoma, 13 people (3.5%) died due to other causes, and one person was excluded from the study. In general, the overall survival rate was 65%. The mean of overall survival was 164.7 ± 12.9 months, with a confidence interval of 95% (139.4-190). According to the Kaplan-Meier method, the survival probability of 1, 2, 3, 5, and 10 years was 86%, 80%, 76%, 69.5%, and 52%, respectively (Figure 1).

Based on the results, the mean overall survival time was significantly higher in women than in men ($P=0.036$). Additionally, 40-49-year-old patients had the longest survival time, and patients over 80 years had the lowest survival time ($P<0.001$). In terms of the disease subgroup, HCL-type NHL had the longest survival time, and T-cell type had the lowest survival time ($P<0.001$). According to the findings, the HCL subgroup had the highest mean survival time, and the T-cell type had the lowest mean survival time ($P<0.001$, Table 1).

In addition, the highest and lowest survival times were related to the third and fifth stages of the disease, respectively. This difference in survival time between the

Table 1. Frequency, Survival Rate, and Mean Survival Time in Patients With Non-Hodgkin’s Lymphoma Based on Demographic and Disease-related Variables

Variable		N (%)	Survival Rates	Mean Survival Time ± Standard Error	P Value
Gender	Men	238 (64)	57.1	125.4 ± 8.6	0.036
	Women	134 (36)	69.4	201.3 ± 19.5	
Age (y)	<30	29 (7.8)	58.6	100.8 ± 27.1	<0.001
	30-39	32 (8.6)	68.8	155.2 ± 19.8	
	40-49	55 (14.8)	74.5	208.5 ± 30.7	
	50-59	81 (12.8)	76.5	146.7 ± 11.3	
	60-69	83 (22.3)	65.1	134.2 ± 12.7	
	70-79	62 (16.7)	54.1	101.6 ± 11.7	
	>80	30 (8.1)	40	60.6 ± 11.5	
Subtypes	B-cell	218 (58.6)	65.6	50.55 ± 3.30	<0.001
	T-cell	23 (6.2)	43.5	34.47 ± 7.6	
	CLL	115 (31.2)	63.5	78.03 ± 5.2	
	HCL	15 (4)	100	102.8 ± 15.4	
Stage of disease	0	57 (15.3)	71.9	170.5 ± 13	<0.001
	I	42 (11.3)	88.1	167.2 ± 14.2	
	II	108 (29)	79.6	198.5 ± 29.8	
	III	61 (16.4)	50.8	74.2 ± 9.5	
Disease recurrence status	IV	89 (23.9)	35.2	67.5 ± 10.6	<0.001
	Yes	43 (11.3)	31	74.2 ± 9.5	
Type of treatment	No	329 (88.7)	69.3	179.7 ± 14.4	<0.001
	Chemotherapy	294 (79)	66.2	173.4 ± 14.1	
	Chemotherapy - radiotherapy	46 (12.4)	50	76.8 ± 9.5	
	Chemotherapy- bone marrow transplant	2 (0.5)	0	28.5 ± 1.5	
	Chemotherapy -radiotherapy- bone marrow transplant	8 (2.2)	37.5	42.1 ± 9	
	Without treatment and under follow-up	22 (5.9)	95.5	156.6 ± 10.9	

Note. CLL: Chronic lymphocytic leukemia; HCL: Hairy cell leukemia.

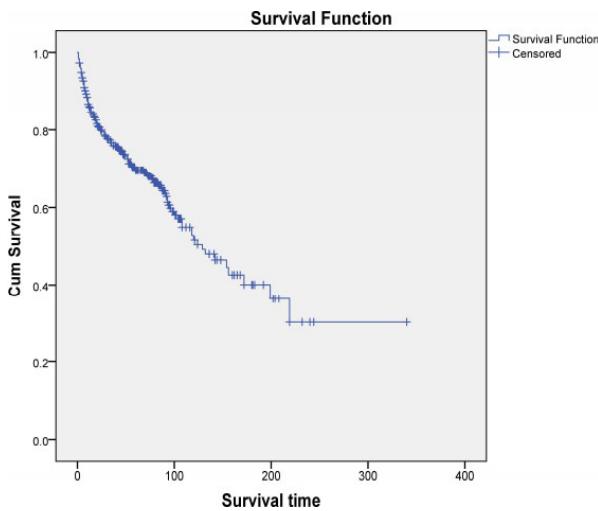


Figure 1. Survival Time in Patients With Non-Hodgkin’s Lymphoma

different stages of the disease was statistically significant ($P < 0.001$). Regarding the type of treatment method, the highest mean survival time was related to patients who had only chemotherapy. The lowest mean survival time was related to patients with chemotherapy and bone marrow transplants, which was statistically significant ($P < 0.001$).

The findings showed that people who had a relapse had a shorter mean survival time ($P < 0.001$, Table 1).

The results demonstrated that the longest mean survival time was associated with patients with involvement in the digestive system, but it was not statistically significant. The shortest survival time was related to patients with involvement in the regions of the chest, which was statistically significant ($P = 0.001$). The relationship between the survival time and involvement in the inguinal ($P = 0.008$) and abdominal-pelvic regions ($P = 0.002$) was also statistically significant (Table 2).

According to the results of the univariate analysis, variables with a significance level of less than 0.2 were entered into the Bayesian parametric survival analysis. The results of the Bayesian parametric survival analysis using the Weibull distribution are presented in Table 3. In the multiple analysis of variables related to the survival rate of NHL, the first significant variable was gender. Thus, it was associated with a lower risk of death in women compared to men ($HR = 0.65$). The following variable was the type of treatment. The risk of death was more than two times higher in patients who received chemotherapy and radiotherapy compared to patients who only used chemotherapy, which was significant

Table 2. Frequency, Survival Rate, and Mean Survival Time in Patients With Non-Hodgkin's Lymphoma According to the Site of Involvement

Site of Involvement		N (%)	Survival Rates	Mean Survival Time \pm Standard Error	P Value
Head and neck	Yes	93 (25)	64.5	122.2 \pm 12	0.132
	No	278 (75)	65.1	168.7 \pm 14	
Axillary	Yes	51 (13.7)	64.7	107.8 \pm 14.2	0.403
	No	320 (86.3)	65	168.4 \pm 13.5	
Inguinal	Yes	37 (9.9)	51.4	70.8 \pm 10.4	0.008
	No	334 (90.1)	66.5	169 \pm 13.3	
Abdominal-pelvic	Yes	84 (22.6)	58.3	71.5 \pm 5.9	0.002
	No	287 (77.4)	66.9	175.1 \pm 14	
Chest	Yes	29 (7.8)	48.3	50.5 \pm 8.1	0.001
	No	342 (92.2)	66.4	170.1 \pm 13.3	
Digestive system	Yes	38 (10.2)	63.2	179.2 \pm 33.5	0.883
	No	333 (89.8)	65.2	134.3 \pm 7.5	
Bone marrow	Yes	175 (47.3)	61.1	133.3 \pm 9.2	0.825
	No	196 (52.7)	68.4	168.5 \pm 21	
Other	Yes	65 (17.5)	63.1	103.6 \pm 12.6	0.03
	No	306 (82.5)	65.4	168.8 \pm 13.5	

according to the credible interval (HR = 2.15). The risk of death was more than three times higher in patients who received chemotherapy, radiotherapy, and bone marrow transplants in comparison to patients who only utilized chemotherapy, which was significant according to the confidence interval (HR = 3.43).

The other variable was the stage of the disease. The risk of death was reduced in patients in stages I and II compared to stage 0, and it was significant (HR = 0.59). However, patients who were in stages III and IV had an increased risk of death compared to patients in stage 0 (HR = 1.7). The next variable was disease recurrence; patients with recurrence had a higher risk of death than those without recurrence. However, it was not significant (HR = 1.37). Regarding the variable of involvement site, patients whose sites of involvement were head and neck had a higher and considerable risk of death than other patients (HR = 1.45). Other involved sites had no significant effect on the survival time.

Discussion

The overall survival rate was 65%, and the mean survival time was 164.7 months, with a standard error of 12.9. Based on the International Prognostic Index for lymphomas, patients over 60, in stages III and IV, with high LDH levels and involved lymph nodes in more than four regions, have a shorter survival time.¹⁸

Gender was the first variable that was examined in this study. In general, women are 30% less affected by NHL than men, respond better to treatment, and, as a result, live longer. The reason for this issue has yet to be definitively found. However, it could be due to the difference in sex hormones or the difference in the immune systems of the

Table 3. Hazard Ratio for the Survival Rate in Patients With Non-Hodgkin's Lymphoma Based on the Parametric Bayesian Survival Model

Variables	Hazard Ratio	Median	95% CI
Age at diagnosis	1.03	1.02	1.02-1.05
Gender			
Men	1		
Women	0.65	0.74	0.044-0.93
Subtypes			
NHL (T-cell)	1		
CLL	0.85	0.67	0.51-1.31
Type of treatment			
Chemotherapy	1		
Chemotherapy -radiotherapy	2.15	2.36	1.22-3.57
Chemotherapy -radiotherapy-bone marrow transplant	3.43	1.32	1.58-6.16
Without treatment and under follow-up	0.42	0.21	0.28-0.62
Disease stage			
0	1		
1	0.58	0.35	0.32-0.97
2	0.59	0.58	0.42-0.78
3	1.79	1.94	1.12-2.65
4	2.87	3.16	2.09-3.57
Disease recurrence status			
No	1		
Yes	1.37	0.76	0.78-2.11
Site of involvement: Head and neck			
Yes	1.45	0.77	1.03-1.99
No	1		
Site of involvement: Inguinal			
Yes	1.44	0.58	0.86-2.36
No	1		
Site of involvement: Abdominal-pelvic			
Yes	1.38	1.25	0.94-1.98
No	1		
Abdominal-pelvic: Chest			
Yes	1.51	0.90	0.85-2.54
No	1		
Abdominal-pelvic: Digestive system			
Yes	0.72	0.70	0.44-1.11
No	1		

Note. HR: Hazard ratio; Note. CLL: Chronic lymphocytic leukemia; NHL: Non-Hodgkin's lymphoma; CI: Confidence interval.

two genders in recovery after surgery.¹⁹

The results of this study also indicated that the number of men suffering from this disease was two times higher than that of women. In a study by Najafi et al, NHL was more common in men than women.²⁰ The findings showed that the survival time of women was significantly longer than that of men, with a mean difference of about 76 months. In another study by Sultan et al, 184 patients with NHL were examined in Pakistan. Their results revealed that

the number of men was three times higher than that of women.²¹ Xie et al also found that in all subgroups, the survival rate in women was slightly higher than in men,⁵ which is in line with the results of another study.²²

The results of this study also confirmed that patients aged 40-49 years had the longest mean survival time, whereas patients over 80 years old had the shortest mean survival time, which was statistically significant. Among the possible reasons for this issue, we can mention the intolerance of therapeutic interventions and their complications due to body exhaustion in elderly patients. It is essential to point out that the clinical stage of disease diagnosis is one of the most important indicators of survival. Optimal treatments can only be performed for people whose disease is in its early stages. Considering that the elderly are most likely in more advanced stages of the disease, it is possible that some treatment procedures cannot be performed for them, and this reduces their mean survival time. In the study by Xie et al, the survival time of the elderly was lower than that of the young patients.⁵ Considering the effect of age on survival time, it is necessary to start treatment measures more urgently for elderly patients. Considering that elderly patients are most likely in more advanced stages of the disease, it is possible that some treatment procedures cannot be performed for them, and this reduces their mean survival time. In the study of Xie et al, the survival time in elderly patients was lower than in young patients.⁵ Considering the effect of age on survival time, it is essential to start treatment measures more urgently for elderly patients.

The results represented that the mean survival time in the HCL subtype was higher and that in the T-cell type, it was less than that of other subtypes, which was statistically significant. A study reported that overall survival in 9 years was 84.6% and 73.4% for B-cell lymphoma and T-cell lymphoma, respectively.²³ Xie et al believe the T-cell subgroup has a worse prognosis than the other subgroups. The mean survival time is shorter than that of the different subgroups because the T-cell subgroup is diagnosed in the advanced stages of the disease.⁵ Among the NHL.B-cell subgroups, the small lymphocytic leukemia subgroup had the highest mean survival time, while the MCL had the lowest mean survival time, which was statistically significant. In the study by Sultan et al, 91.3% of patients had NHL.B-cell, and 8.6% had NHL.T-cell. Further, 85.8% had advanced lymphoma.²¹

According to the findings of this study, there was a significant relationship between survival time and involvement in the inguinal region, namely, abdominal-pelvic. Furthermore, the shortest survival time was related to the patient with chest involvement (with a mean of 50 months). Moreover, about 30% of patients were in stage III, and this group had the longest survival time compared to other patients (with a mean of 198 months). The patients in stage IV had the shortest survival time (with a mean of 67 months), which was statistically significant.

Currently, different treatments are used in Iran and

around the world for NHL, of which chemotherapy is the most common. In the current study, 79% of patients were treated only with chemotherapy, and the longest survival time was related to them. At the same time, the patients who were treated with bone marrow transplants and chemotherapy had the shortest survival time. Chemotherapy is often utilized for patients with limited lesions. Patients with limited lesions are usually in the early stages of the disease, and there is less damage to the body. It seems reasonable that patients in the early stages of the disease had a higher survival time than patients with more lesions.²⁴

In our study, the Bayesian parametric regression model's results indicated significant effects on patients' survival time based on variables such as gender, type of treatment, disease stages, and site of involvement. A recent study by Singh et al explored factors influencing survival rates in patients with NHL.²⁵ The findings revealed that several factors were significantly associated with patient survival. Specifically, the analysis showed that patients over 65 years of age had a higher risk of mortality (HR=2.87) compared to those under 65. Additionally, patients with stage 4 cancer had a higher risk of mortality (HR=1.93) in comparison to those with stage 1 disease. The study findings also represented that males were more likely to experience poor survival outcomes (HR=1.17) than females. Furthermore, the results indicated that patients who received chemotherapy and surgery as treatment had a significantly lower risk of mortality (HR=0.26) compared to those who received no treatment.²⁵

The findings of this study demonstrated that if patients are identified at an early stage, they have the best chance of survival. In CLL patients, the best survival is achieved without treatment. At the same time, chemotherapy offers the best survival for other types of cancer.

Conclusion

In this study, the type of treatment, stage of disease diagnosis, gender, and involvement site were the most important prognostic factors for NHL. In CLL patients, the best survival is achieved without treatment. At the same time, in other types of cancer, chemotherapy suggests the best survival.

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Authors' Contribution

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Supervision: Hossein Fallahzadeh.

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Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

In this study, the information extracted from the patient's record files was utterly confidential, and a trained expert was used to contact the patients or their families. The present study has ethical approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Iran (code IR.SSU.SPH.REC.1399.219).

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