# Prognostic Factors Affecting the Clinical Course of non-Hodgkin's Lymphomas

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**ABSTRACT**

Non-Hodgkin's lymphoma (NHL) includes lymphoproliferative malignant diseases with a wide variety of clinicopathologic appearances. The aim of our study was to analyse the critical prognostic factors that effect clinical picture in NHL patients. In this study, we retrospectively evaluated the effects of the clinical characteristics, International Prognostic Index (IPI) parameters (age, stage, performance status, extranodal sites, and serum lactate dehydrogenase), and other prognostic parameters (bulky disease, grade of disease, "B" symptoms, and ß-2 microglobulin levels) on overall survival (OS) and disease-free survival (DFS) in NHL patients who have been diagnosed in our department. Stage of the patients was not related with OS and DFS. But higher grade and IPI levels were found to be independent prognostic factors that predict OS. According to clinical and laboratory parameters, only age and bulky disease were found to be an independent risk factor that predict OS. In conclusion, our results suggest that, using only the stage and/or grade of the disease does not completely correlate with the prognosis. Stage and grade could be significant indicators, if they are evaluated along with other prognostic factors.

**Keywords:** NHL, Clinical characteristics, Prognostic factors, IPI

**ÖZET**

**Non-Hodgkin Lenfomada Klinik Seyri Etkileyen Prognostik Faktörler**

Non-Hodgkin lenfomalar (NHL), değişik klinikopatolojik görünümlere sahip bir grup lenfoproliferatif malign hastalığı kapsayan bir terimdir. Bu çalışmamızın amacı NHL'deki klinik tabloyu etkileyen prognostik faktörleri saptamaya çalışmaktı. Çalışmamızda Hacettepe Üniversitesi Tıp Fakültesi Hematoloji Ünitesinde 2000-2005 yılları arasında NHL tanısı alan hastaların klinik özelliklerini, "Enternasyonel Prognostik İndeks" (IPI) içerisinde yer alan parametrelerin (yaş, evre, performans statusu, ekstranodal tutulum, ve serum laktat dehidrogenaz düzeyi) yanı sıra bu indeksde bulunmayan diğer parametrelerin (kütlesel hastalık, hastalık derecesi, "B" semptomları ve ß-2 mikroglobulin düzeyi) genel sağkalım (GS) ve hastalıksız sağkalım süresi (HYS) ve tedavi sonuçları üzerindeki etkilerini retrospektif olarak inceledik. Hastalık evresi GS ve HYS üzerine etkili bulunmadı. Ancak yüksek hastalık derecesi ve IPI skorları GS üzerine etkili bağımsız bir risk faktörü olarak saptandı. Klinik ve laboratuvar parametrelerinden sadece yaş ve kütlesel hastalık GS üzerine etkili idi. Sonuç olarak, prognozu öngörmede hastalık evre ve/veya derecesinin tek başına kullanılmasından ziyade diğer prognostik faktörlerle birlikte kullanılmasının daha sağlıklı sonuçlar vereceği görüşüne varılmıştır.

**Anahtar Kelimeler:** NHL, Klinik özellikler, Prognostik faktörler, IPI

## INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoid malignancies that have several different morphologic, immulogic and genetic features. Non-Hodgkin's lymphomas represent about 3-4% of all malign neoplastic disorders and 60% of all lymphomas.[1,2] Overall survival ranges between several months to decades. Disparities in clinical pattern between patients exhibits a need for a prognostic system as a guide for choosing a treatment protocol.

Studies in recent years have permitted more precise disease classifications and recognition of factors that can predict prognosis and response to treatment. In general, a variety of clinical characteristics were consistently associated with poor outcome: the age at diagnosis (>60 years), low performance status, presence of systemic (B) symptoms, advanced disease, bulky tumor dimension (≥10 cm), the sites extranodal sites of disease (≥3), bone marrow involvement, and high lactate dehydrogenase (LDH) levels.[3] It is critically important to analyse these prognostic factors in every clinical step of the disease.

Although there were several risk factors that effects prognosis, adults with aggressive non-Hodgkin's lymphoma who were treated between 1982 and 1987 with combination-chemotherapy regimens were evaluated for clinical features predictive of prognosis and 5 independent risk factors were determined; age, stage, number of extranodal sites of the disease, performance status and serum LDH levels. This model later defined as International Prognostic Index (IPI).[4] IPI scores are commonly used to predict the prognosis of NHL patients.[4,5] There are also some other prognostic factors that effects prognosis, so it is favorable for all centers to determine their own results.

The aim of this study is to analyse the critical prognostic factors which effect clinical outcomes in NHL patients. For that reason, patients who were diagnosed as NHL at our department were retrospectively evaluated. The effect of clinical characteristics, IPI parameters, bulky disease, grade of the disease, B symptoms, ß-2 microglobulin levels on overall survival (OS) and disease-free survival (DFS) were investigated. Although the clinicopathology and population characteristics of NHL varies between regions, it is strongly recommended for the national clinics to make single/multicenteral studies to better understanding of NHL and in the selection of appropriate therapeutic approaches for individual patients.

## PATIENTS AND METHODS

### Characteristics of the Patients

Sixtyone patients (37 females, 24 males; aged 54.7±14.6 years) who were diagnosed as NHL between 2000 and 2005 at Hematology Department of Hacettepe University Hospital, were retrospectively evaluated. All patients had a biopsy-proven diagnosis of low, intermediate or high-grade NHL according to the International Working Formulation. All patients were staged according to the Ann Arbor classification. Clinical staging included a full history and physical examination, full blood count and erythrocyte sedimentation rate, biochemical profile including liver function tests and serum lactate dehydrogenase, unilateral bone marrow aspirate with biopsy, chest radiograph, chest and abdominopelvic computed tomography scan.

The clinical characteristics evaluated for potential prognostic importance were sex, age, performance status [according to the Eastern Cooperative Oncology Group (ECOG) scale, in which 0 indicated that the patient had no symptoms; 1, the patient had symptoms but was ambulatory; 2, the patient was bedridden less than half the day; 3, the patient was bedridden half the day or longer; and 4, the patient was chronically bedridden and required assistance with the activities of daily living], tumor stage, B symptoms [fever, loss of more than 10% of total body weight, night sweats], sites of lymphomatous involvement, number of extranodal disease sites, size of the largest tumor, and serum concentrations of LDH and ß-2 microglobulin. The recorded sites of extranodal lymphomatous involvement included the bone marrow, gastrointestinal tract, lung, central nervous system, liver, and other sites. Bulky disease was defined as masses or lesions measuring greater than 10 cm in greatest diameter at commencement of therapy. Response status was assessed by standard World Health Organization (WHO) criteria. Survival was calculated from the date of starting treatment. Disease-free survival was calculated from the time of confirmed establishment of comp-

**Table 1.** Patient characteristics

| | | Total no: 61 | |
|---|---|---|---|
| | | n | % |
| Mean age (years) | | 54.7±14.6 | |
| Sex | Male | 24 | 60.7 |
| | Female | 37 | 39.3 |
| "B" symptoms | | 31 | 51.8 |
| Primary site | Nodal | 41 | 67.2 |
| | Extranodal | 20 | 32.8 |
| Bulky disease (>10 cm) | | 17 | 27.9 |
| Stage | I | 5 | 8.2 |
| | II | 14 | 22.9 |
| | III | 13 | 21.3 |
| | IV | 29 | 47.5 |
| Grade | Low | 11 | 18 |
| | Intermediate | 22 | 36.1 |
| | High | 20 | 32.8 |
| | Unknown | 8 | 13.1 |
| IPI scores | 0 | 3 | 4.9 |
| | 1 | 4 | 6.6 |
| | 2 | 16 | 26.2 |
| | 3 | 19 | 31.1 |
| | 4 | 11 | 18 |
| | 5 | 8 | 13.1 |

lete remission to the first evidence of disease progression or recurrence.

Patients were assigned to one of four risk groups on the basis of their number of presenting IPI risk factors: 0 or 1, low risk; 2, low-intermediate risk; 3, high-intermediate risk; or 4 or 5, high risk.

Eight patients received initial involved-field irradiation followed by adjuvant chemotherapy with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP). Forty-three patients received alone chemotherapy with CHOP. Seven patients received initial chemotherapy with IIVP (idarubicin, ifosfamide and etoposide). Five patients received initial chemotherapy with DHAP (dexamethasone, high-dose cytarabine, cisplatin). One patient with central nervous system involvement received intrathecal methotrexate. Thirteen patients, in whom CHOP performed as an initial therapy received rituximab as a second-line therapy.

**Table 2.** Laboratory values at initial diagnosis

| Parameter | Mean | n |
|---|---|---|
| Hemoglobin (g/dl) | 10.9±2.7 | 61 |
| Hematocrit (%) | 33.2 ± 1.42 | 61 |
| Leukocyte (/mm$^3$) | 6350 ± 1800 | 61 |
| Platelet count (/mm$^3$) | 272000 ±154000 | 61 |
| Sedimentation rate (mm/h) | 50.7±34.9 | 57 |
| ß-2 microglobulin (ng/dl) | 3625 ±1823 | 51 |
| Lactate dehydrogenase (IU/L) | 520 ± 170 | 61 |

### Statistical Analysis

Survival was calculated by Kaplan and Meier's method. Differences in survival between prognostic groups was evaluated in univariate analysis by the log-rank test, and the respective influence on survival of the different variables was considered to be significant at $p < 0.05$. All calculations were performed using the SPSS 10,0 for Windows.

## RESULTS

The clinical characteristics and laboratory findings of the patients are depicted in Table 1 and Table 2 respectively.

Stage of the patients were not related with OS and DFS. But higher grade and IPI risk groups were found to be an independent prognostic factor that predict OS (p= 0.013 and 0.0069, respectively) (Figures 1 and 2). OS and DFS of the patients according to their stage, grade, and IPI risk groups are depicted in Table 3.

According to clinical and laboratory parameters, only age and bulky disease were found to be an independent risk factor that predict OS (p= 0.048 and 0.006, respectively) (Table 4).

There were no statistically significant difference between patients who were received only CHOP or CHOP+rituximab according to OS and DFS (p= 0.32 ve p= 0.291, respectively).

## DISCUSSION

In this study, we found that according to OS and DFS, only older age (>60 years) and bulky tumor dimension were negatively correlated with OS (in-

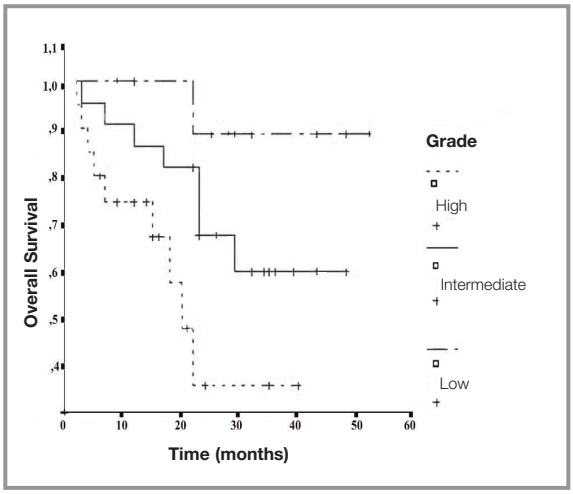


**Figure 1.** Survival related to grade of the disease

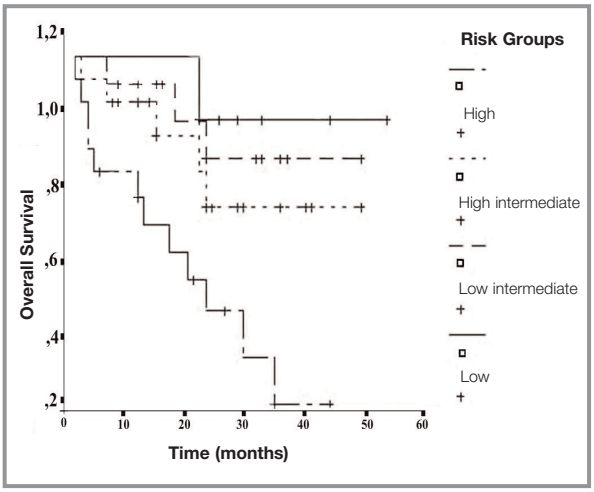


**Figure 2.** Survival related to IPI risk groups

dependent from each other). Kushlan et al.[6] determined tumor size as the sole significant prognostic factor in stage II diffuse histiocytic lymphoma. Cabanillas and Burke[7] have also identified tumor bulk as a poor prognostic factor. In addition to these parameters, factors that are usually accepted to have prognostic value include B symptoms, performance status, primary site of involvement, hemoglobin and LDH levels.[8,9-11] But in our study we found no relation between these factors and OS or DFS.

Although the international prognostic index was specifically developed to predict outcome in patients with aggressive non-Hodgkin's lymphoma, it may also have prognostic value in patients with lymphoma that is histologically more indolent.[4,5] In this study, after retaining patients to four risk groups (low, low-intermediate, high-intermediate, high) defined by the international prognostic index, OS and DFS of the patients were calculated. The four risk groups had distinctly different overall survivals (Table 3) (p= 0.0069). Although there were a slight decrease in disease-free survival while the risk groups increase, this was statistically insignificant (p= 0.21). Lopez-Guillermo et al.[5] found that

**Table 3.** Overall and disease-free survivals of the patients according to stage, grade, and IPI risk groups

| | | **Overall survival** (months) | **Disease-free survival** (months) |
|---|---|---|---|
| Stage | I | 32.4±2.33 | 36.4±2.33 |
| | II | 45.63±4.14 | 38.01±4.68 |
| | III | 26.77±4.81 | 34.85±4.03 |
| | IV | 20.9±3.49 | 23.79±1.24 |
| | p | 0.18 | 0.821 |
| Grade | Low | 48.67±3.14 | 44.33±3.46 |
| | Intermediate | 36.01±3.46 | 38.57±2.32 |
| | High | 22.88±3.79 | 24.5±2.34 |
| | p | 0.013 | 0.0682 |
| Risk group defined by International Prognostic Index | | | |
| | Low | 47.71±3.97 | 39±3.70 |
| | Low- intermediate | 40.75±3.72 | 31.7±2.17 |
| | High- intermediate | 36.83±4.16 | 34.53±4.74 |
| | High | 22.1±3.59 | 25.32±3.21 |
| | p | 0.0069 | 0.21 |

**Table 4.** Overall and disease-free survivals of the patients according to clinical parameters

| Parameter | | Overall survival (months) | Disease-free survival (months) | n |
|---|---|---|---|---|
| Age | <60 | 39.96±3.03 | 38.91±2.90 | 39 |
| | >60 | 26.01±3.69 | 37.0±4.24 | 22 |
| | p | 0.048 | 0.287 | |
| Sex | Female | 42.95±3.14 | 33.5±2.98 | 24 |
| | Male | 39.82±3.4 | 44.5±2.29 | 37 |
| | p | 0.053 | 0.112 | |
| Bone marrow | (+) | 37.47±4.83 | 36.03±0.48 | 19 |
| involvement | (-) | 33.34±2.91 | 39.91±3.20 | 42 |
| | p | 0.765 | 0.745 | |
| Bulky disease | (+) | 22.98±4.49 | 34.63±4.93 | 17 |
| | (-) | 40.1±2.8 | 40.5±2.62 | 44 |
| | p | 0.006 | 0.359 | |
| "B" symptoms | (+) | 30.8±3.12 | 38.3±2.43 | 30 |
| | (-) | 36.07±3.56 | 39.3±3.18 | 31 |
| | p | 0.876 | 0.81 | |
| ECOG* | 0 | 32.2±3.4 | 33.6±3.45 | 5 |
| Performance | 1 | 41.6±3.9 | 33.19±3.14 | 19 |
| Status | 2 | 29.79±5.2 | 41.4±4.11 | 16 |
| | 3 | 28.4±3.5 | 39.25±3.15 | 17 |
| | 4 | 22.75±5.4 | 29.2±3.2 | 4 |
| | p | 0.584 | 0.47 | |
| Nodal involvement | (+) | 36.57±3.26 | 37.8±3.14 | 41 |
| | (-) | 27.2±2.66 | 33.2±0.65 | 20 |
| | p | 0.96 | 0.113 | |
| LDH (IU/L) | Normal | 39.6±6,8 | 33.5±1.77 | 8 |
| | High | 35.98±2,8 | 40.8±2.4 | 53 |
| | p | 0.58 | 0.92 | |
| ß–2 microglobulin | Normal | 45.0±4.38 | 40.2±4.8 | 9 |
| | High | 28.6±2,63 | 36.4±2.45 | 42 |
| | p | 0.15 | 0.94 | |

*ECOG: Eastern Cooperative Oncology Group

after a 20 years of follow-up in 125 patients with low-grade lymphoma, the low-risk group had a ten-year overall survival of 73.6 percent, whereas the high-risk group had an overall survival rate of only 11.2 percent. They suggested that IPI has a negative effect on overall survival. The most important prognostic factors in IPI are believed to be the LDH and performance status.[4,5] According to this index, patients in low risk group has a cure chance of >50%, but in high risk cure chance significantly decreases (<50%). The identification of different risk groups would also aid in the design and interpretation of therapeutic trials.[4]

IPI system was unable to include other markers such as immunophenotyping, ß-2 microglobulin or bcl-2 protein expression. Prognostic significance of T-cell immunophenotype has been shown for large-cell lymphoma, other than anaplastic, and should be taken into consideration when choosing treatment.[13] In the near future, we can expect that new biological prognostic factors will be identified and that their significance will be compared with the clinical IPI.[3,14]

Clinical staging is important in estimating prognosis, appropriate thearapeutic selection, and response to treatment.[8] The standard staging system for NHL is the same as that proposed for Hodgkin's disease at the Ann Arbor conference in 1971.[15] Its main use is to differentiate localized stage I and II disease from the disseminated stages III and IV. For

some subtypes, especially indolent lymphomas, widespread disease is characteristic without necessarily conferring a poor prognosis.[3] Also, staging does not take into account certain prognostic factors like bulky disease, age and some prognostically important sites of involvement, especially the central nervous system and bone marrow. Future descriptive and analytic investigations should evaluate NHL risks according to subtype, as defined by histology and new classification criteria.[16] In our study, although histologic grade of the patients were found to be a significant predictor for OS, stage of patients was not correlated with OS and DFS. There is still no evidence in the current literature to support or refute the relationship between OS and stage and/or grade of the disease.[17-20] Bitran et al.[21] found that relapse-free survival was related to the number of sites of involvement in 20 patients with pathologic stages I and II disease. Alici et al.[22] have identified high-grade histology as a poor prognostic factor. For that reason in clinical practice, it is not possible to estimate prognosis only with stage and/or grade of the disease in NHL patients. Stage and grade can provide a significant result, if they are evaluated along with other prognostic factors.

Since NHL has an heterogeneous and variable clinicopathology, treatment strategies varies. In our study, we found that CHOP was the most commonly used protocol as a first- line therapy (83.6%). CHOP was preferred especially in advanced stages whereas fludarabine was used in early stages. Rituximab was used in 21.3% of the patients. We were not able to detect a relationship between different chemotherapy regimens and OS and DFS because the majority of the patients had been treated with CHOP regimen. In recent years, it has been shown that CHOP plus rituximab is superior to CHOP in patients with diffuse large B-cell lymphoma.[23] Newer treatment approaches (e.g. radiolabelled monoclonal antibodies, allogeneic stem cell transplantation, idiotype vaccines) have been tried to improve survival and ultimately provide a cure for patients with NHL, but R-CHOP is still the first treatment option in a variety of NHL subtypes.[24-26]

Despite all the technological advances of modern medicine, overall survival is, however, still not significantly improved in NHL patients. It is important to classify patients according to their prognostic markers at initial diagnosis. While evaluating the prognosis of a patient, it is adviced to assess both clinical parameters like stage and grade of the disease as well as other prognostic factors.

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