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Clinical and pathological evaluation of histopathological subtypes in patients with non-Hodgkin's lymphoma

Feray Tabakan[1], Erdinc Nayir[2], Ali Arican[3]

[1] Department of Internal Medicine, Mersin University, Faculty of Medicine, Mersin, Turkey
[2] Department of Medical Oncology, Kahramanmaras Necip Fazil State Hospital, Kahramanmaras, Turkey
[3] Department of Medical Oncology, Acibadem University Faculty of Medicine, Istanbul, Turkey

ABSTRACT

Objectives. Non-Hodgkin Lymphomas (NHLs) are tumours of the lymphoid system which originate from lymph nodes or extranodal lymphatic tissue. Since they represent a heterogeneous group of diseases, it is very important to determine prognostic factors apart from staging and identification of the patients with poor prognosis. The objective of our study is to investigate clinical characteristics, treatments applied, and their outcomes, survival rates, and prognostic factors which may be effective on survival. ***Methods.*** Clinical characteristics, treatments applied, and their outcomes, survivals, and prognostic factors which may be effective on the survival in 230 patients who were diagnosed as NHL, and consulted to our center between the years 2002, and 2015 were retrospectively evaluated. ***Results.*** Median age of our patients (male, 54.8 %, and female, 45.2 %) was 57 years. The most frequently seen histopathological subtype was diffuse large β cell lymphoma. We have seen that IPI score, β symptom, levels of LDH, albumin, β2 microglobulin, and lymphocyte counts are significant prognostic factors. Stomach was the most frequently involved extranodal organ. Advanced stage, higher IPI score, extranodal organ involvement were found to be correlated with shorter survival times. ***Conclusion.*** Everyday developments occur in the diagnosis, classification, and treatment of NHL. Therefore, it is important for medical centres to evaluate their treatment outcomes, and prognostic factors affecting their survival rates.

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Keywords: Non-Hodgkin Lymphoma, survival rate, IPI score

Introduction

Non-Hodgkin's lymphoma (NHL) is a clonal proliferative disease of B, T or natural killer cells which originate from lymph nodes or extranodal lymphatic tissue [1]. NHL comprises 4% of newly diagnosed cancer, and 90 % of lymphomas. 90% of NHLs are β-cell lymphomas. Clinical features of NHL demonstrate changes with geographical factors. Determination of the characteristics of the patients living in different regions, and definition of different prognostic parameters are very important [2, 3]. Since NHL represents a very heterogeneous disease group, determination of prognostic factors, and

Address for correspondence:
Erdinc Nayir, M.D. Department of Medical Oncology, Kahramanmaras Necip Fazil state Hospital, Kahramanmaras, Turkey
E-mail: drerdincnyr@gmail.com
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identification of patient groups with poor prognosis have a crucial importance [4].

Posttreatment complete response in NHL is around 60-80%, and median 5-year survival rate is over 55 percent [5]. Magnificent developments and innovations have been recorded in the diagnosis, classification, staging, and treatment of NHL. Evaluation of the treatment results of medical centres carries utmost importance.

The objective of our study is to investigate the importance of clinical characteristics, treatments applied, and their outcomes, survival rates, and prognostic factors which might affect survival rates of the patients who were referred to our Department of Medical Oncology and Haematology from any outpatient clinic of Mersin University Hospitals of Faculty of Medicine with the diagnosis of NHL.

Methods

A total of 278 patients were referred to the Department of Medical Oncology and Haematology with the established diagnosis of NHL between the years 2002 and 2015. In consideration of 20 % loss of data in medical files, we planned the study population to be at least 230 patients. Approval of the Mersin University Ethics Committee was obtained for the study. Clinical characteristics, treatments applied, and their outcomes, survivals, and prognostic factors which may be effective on the survival were retrospectively evaluated.

From patient files demographic, clinical, biochemical (albumin, lymphocyte counts, LDH, uric acid, β-microglobulin levels), histopathological findings, treatments applied, and their results, presence of extranodal involvement, and β-symptoms were recorded. For B symptoms, fever (>38°C), marked night sweats, and >10% weight loss during the previous 6 months relative to baseline were taken as a basis. For clinical staging of the disease Ann Arbor classification was used. Histological classification was based on WHO (the World Health Organization) criteria. International Prognostic Index (IPI) scores were calculated. From patient files information about treatments of the patients, and follow-up periods were obtained. Living status of the patients who were lost to follow-up was learnt via phone contact with the patients. WHO criteria were considered for the evaluation of responses.

Statistical Analysis

Categorical data were summarized as numbers, and percentages, while using descriptive statistical methods continuous data were expressed as mean ± standard deviation. In intergroup comparisons regarding patient ages independent two groups t test was used $p<0.05$ was set as the level of significance.

In the present study which followed up patients with non-Hodgkin lymphoma, we aimed to calculate mortality, and survival rates. In survival analyses, the cause of failure was determined as mortality among other parameters (mortality, remission, recurrence etc.). Survival analysis was evaluated by means of Kaplan-Meier method. As an outcome of this analysis, in summary statistics, median survival times were used. In groups which demonstrated differences, the group under higher risk was determined, and interpreted using hazard ratio.

Results

A total of 230 patients (female, n=104; 45.2%, and male, n=126; 54.8%) were included in the study. General characteristics of the patients are given in Table 1.

At the time of diagnosis, mean ages of all cases, female, and male population were 57±15.78 (16-87 years); 57±14.69, and 56±16.66 years, respectively, without any statistically significant difference between genders ($p=0.467$).

At the time of diagnosis, mean IPI scores were 0 in 27 (11.8%), 1 in 57 (24.9%), 2 in 56 (24.5%), 3 in 60 (26.2%), 4 in 26 (11.4%), and 5 in 3 (1.3%) patients.

Fifty-nine (25.9%) patients underwent diagnostic surgery. Most frequently splenectomy (31.7%), tonsillectomy (20%), excision of the mass (16.7%), resection of small bowel/colon (10%), orchiectomy/ovarectomy (8.3%), and parathyroidectomy (5%) were performed.

At the time of diagnosis, based on Ann Arbor staging system, the patients were in Stages I (n=39; 17.4%), 2 (n=42; 18.8%), 3 (n=53; 23.7%), and 4 (n=90; 40.2%). In 98 (42.6%) cases β-symptom was seen. Splenic involvement in 36 (15.7%), and tonsillar involvement in 15 (6.5%) cases were seen.

The most frequently histopathological subtypes in order of decreasing frequency were as follows: diffuse large β-cell lymphoma (DLBCL, 43.2%), B-cell

lymphoma (15.4%), follicular lymphoma (FL, 9.7%), mantle cell lymphoma (MHL, 7.5%), T-cell lymphoma (5.3%). Based on WHO classification histopathological subtypes are given in Table 2.

Table 1. The data of the patients

Data	n (%)
Gender (Female)	104 (45.2)
Age (≥60 years)	115 (50)
IPI	
0	27 (11.8)
1	57 (24.9)
2	56 (24.5)
3	60 (26.2)
4	26 (11.4)
5	3 (1.3)
Stage	
I	39 (17.4)
II	42 (18.8)
III	53 (23.7)
IV	90 (40.2)
β-symptom (+)	98 (42.6)
Splenic involvement (+)	36 (15.7)
Tonsillar involvement (+)	15 (6.5)
Bone marrow involvement (+)	44 (32.8)
Extranodal involvement (+)	100 (43.9)
LDH (≥380 U/L)	43 (22.3)
Albumin (<3.5 g/dL)	41 (21.5)
ß2 microglobulin (≥3000 ng/mL)	43 (36.4)
Uric acid (≥5.7 mg/dL)	62 (34.6)
Lymphocytes (≥1500 mm^3)	128 (60.3)

IPI= International Prognostic Index, LDH=lactate dehydrogenase

At the time of diagnosis bone marrow involvement was seen in 44 (32.8 %) cases. Albumin levels were ≥3.5 g/dL (n= 150; 78.5%) or below (n= 41; 21.5%) 3.5 g/dL. LDH levels were ≥380 U/L (n=43; 22.3%) or below (n=149; 77.7%) 380 U/L. ß2 microglobulin value was ≥3000 ng/mL in 43 (36.4%), and below this value in 75 (63.6%) cases. Uric acid levels were ≥ 5.7 mg/dL in 62 (34.6%), and <5.7 mg/dL in 117 (65.4%) cases. Lymphocyte counts were ≥ 1500/mm3 in 128 (60.3%), and lower that level in 84 (39.7%) cases.

Extranodal involvement was seen only in 100 (43.9%) cases. The distribution of extranodal involvement is given in Table 3.

Treatment Response Rates

The patients received cyclophosphamide+hydroxy doxorubicin+vincristine (Oncovin®)+prednisone (CHOP) (n=18; 10%), rituximab-CHOP (R-CHOP) (n=134; 74.4%), and other chemotherapy (n=15; 8.3%) regimens.

Table 2. Distribution of patients' diagnosis according to histopathological subtypes

Histopathological Subtypes	n (%)
Diffuse large β-cell lymphoma	98 (43.2)
Mantle cell lymphoma	17 (7.5)
Follicular lymphoma	22 (9.7)
B-cell lymphoma	35 (15.4)
T-cell lymphoma	12 (5.3)
Small lymphocytic lymphoma	7 (3.1)
Lymphoblastic lymphoma	1 (0.4)
Malignant lymphoma	10 (4.4)
Marginal zone lymphoma	11 (4.8)
Burkitt lymphoma	2 (0.9)
Mixed type lymphoma	2 (0.9)
Anaplastic large B-cell lymphoma	7 (3.1)
MALT lymphoma	2 (0.9)
Natural Killer cell lymphoma	1 (0.4)

MALT= mucosa associated lenfoid tissue

Complete, and partial treatment response rates were achieved in 120 (62.5%), and 34 (17.7%) patients, respectively, while 37 (19.3%) patients did not respond to treatment. Hundred and seven patients (49.1%) exited, and 111 (50.9%) patients survived.R-CHOP or CHOP therapy achieved complete response rates in 86 (69.4 %), and 7 (41.2%) patients, respectively. Treatment response rates based on chemotherapeutic regimens are given in Table 4.

Tablo 3. Extranodal involvements

Affected organs	%
Stomach	15
Lungs	13.5
Small bowel/colon	13.5
Nasopharynx	12.4
Liver	9
Extremities	6.7
Vertebra	5.6
Brain	4.5
Parotid gland	3.4
Eyes	3.4
Ovary/ testis	3.4
Thyroid	3.4
Retroperitoneum	1.1
Breast	1.1
Kidney	1.1

Table 4. Treatment response rates according to chemotherapy regimens

Chemotherapy Protocols	Response	n (%)
R-CHOP	Complete response	86 (69.4)
	Partial response	18 (14.5)
	No response	20 (16.1)
CHOP	Complete response	7 (41.2)
	Partial response	3 (17.6)
	No response	7 (41.2)

CHOP= cyclophosphamide, hydroxy doxorubicin, vincristine (Oncovin®), prednisone, R-CHOP= rituximab + CHOP

Complete response rates were achieved in patients with IPI scores of 0 (n=17; 81%), 1 (n=38; 77.6%), 2 (n=31; 68.9%), 3 (n=23; 44.2%), and 4 (n=10; 47.6%). While in patients with IPI score of 5, one patient (33.3%) gave partial response, and 2 (66.7%) patients didn't respond to treatment. Treatment response rates based on IPI scores, and disease stages are shown in Tables 5, and 6.

Table 5. Response rates based on IPI scores

IPI Score	Response	n (%)
0	Complete	17 (81)
	Partial	1 (4.8)
	No	3 (14.3)
1	Complete	38 (77.6)
	Partial	3 (6.1)
	No	8 (16.3)
2	Complete	31 (68.9)
	Partial	5 (11.1)
	No	9 (20)
3	Complete	23 (44.2)
	Partial	17 (32.7)
	No	12 (23.1)
4	Complete	10 (47.6)
	Partial	7 (33.3)
	No	4 (19)
5	Complete	0
	Partial	1 (33.3)
	No	2 (66.7)

IPI= International Prognostic Index

Female patients gave complete (n=61; 68.5%) or partial (n=12; 13.5%) responses to treatment, while 16 (18%) female patients did not respond to the treatment at all. Male patients gave complete (n=59; 57.3%) or partial (21.4%) response to treatment, while 22 (21.4%) male patients did not respond to treatment. Treatment response rates based on gender of the patients are given in Table 7.

Table 6. Response rates based on disease stage

Stage	Response	n (%)
I	Complete	0
	Partial	24 (82.8)
	No	5 (17.2)
II	Complete	31 (83.8)
	Partial	4 (10.8)
	No	2 (5.4)
III	Complete	19 (45.2)
	Partial	11 (26.2)
	No	12 (28.6)
IV	Complete	43 (54.4)
	Partial	18 (22.8)
	No	18 (22.8)

Table 7. Response rates according to gender

Gender	Response	n (%)
Female	Complete	61 (68.5)
	Partial	12 (13.5)
	No	16 (18)
Male	Complete	59 (57.3)
	Partial	22 (21.4)
	No	22 (21.4)

Patients with β-symptom gave complete (n=43; 51.8%) or partial (n=18; 21.7%) responses to treatment, while 22 (26.5%) of them did not respond

to the treatment at all.

Patients with albumin levels ≥3.5 g/dL gave complete (n=97; 74%) or partial (n=20; 15.3%) responses to treatment, while 14 (10.7%) patients did not respond to treatment at all.

In patients with LDH levels above 380 U/L, complete (n=23; 56.1%), and partial (n=9; 22%) response rates were achieved, while 9 (22%) patients were unresponsive to treatment.

In patients with ß2 microglobulin levels of ≥3000 ng/mL, complete (n=23; 57.5%), and partial (n=5; 12.5%) response rates were achieved, while 12 (30%) patients did not respond to treatment. In patients with ß2 microglobulin levels of <3000 ng/mL complete (n=55; 83.3%) and partial (n=9; 13.6%) response rates were achieved, while 2 (3%) patients did not respond to treatment.

Patients with uric acid levels ≥5.7 mg/dL gave complete (n=30; 57.7%) or partial (n=11; 21.2%) responses to treatment, while 11 (21.2%) patients did not respond to the treatment at all. Among patients with uric acid levels of <5.7 mg/dL, complete or partial treatment response rates were achieved in 74 (72.5%), and 15 (14.7%) patients, respectively.

Table 8. Treatment response rates according to laboratory results

Test	Response	n (%)
Albumin ≥ 3.5 g/dL	Complete	97 (74)
	Partial	20 (15.3)
	No	14 (10.7)
Albumin < 3.5 g/dL	Complete	17 (47.2)
	Partial	8 (22.2)
	No	11 (30.6)
LDH ≥ 380 U/L	Complete	23 (56.1)
	Partial	9 (22)
	No	9 (22)
LDH < 380 U/L	Complete	90 (70.3)
	Partial	20 (15.6)
	No	18 (14.1)
Uric acid ≥ 5.7 mg/dL	Complete	30 (57.7)
	Partial	11 (21.2)
	No	11 (21.2)
Uric acid < 5.7 mg/dL	Complete	74 (72.6)
	Partial	15 (14.7)
	No	13 (12.7)
β2 microglobulin ≥ 3000 mg/L	Complete	23 (57.5)
	Partial	5 (12.5)
	No	12 (30)
β2 microglobulin < 3000 mg/L	Complete	55 (83.3)
	Partial	9 (13.6)
	No	2 (3)
Lymphocytes ≥ 1500	Complete	80 (69.6)
	Partial	22 (19.1)
	No	13 (11.3)
Lymphocytes < 1500/mm^3	Complete	40 (54.8)
	Partial	12 (16.4)
	No	21 (28.8)

LDH= lactate dehydrogenase

However, 13 (12.7%) patients did not respond to treatment at all.

Patients with lymphocyte counts of ≥1500 mm3 complete (n=80; 69.6%) or partial (n=22; 19.1%) respond rates were achieved, while 13 (11.3%) patients did not respond to treatment. Patients with lymphocyte counts of <1500 mm3 complete (n=40; 54.8%) or partial (n=12; 16.4%) respond rates were achieved, while 21 (28.8%) patients did not respond to treatment.

Survival analyses

From a total of 230 study patients, 217 of them were included in the survival analysis. Median survival time of the patients was 60 months, while 5-year-survival rate was 48.1 percent.

A statistically significant difference was not found between the survival times of female, and male patients with non-Hodgkin lymphomas (p=0.77). Median survival times in female and male patients were 72, and 60 months, respectively. Five-year survival rates in female and male patients were 50, and 46%, respectively.

A statistically significant difference was found between patients with and without β symptoms as for survival times (p=0.002). Median survival times in patients with, and without β symptom were 48, and 72 months, respectively. The mortality risk in patients with β symptom was 1.93 times higher when compared with those without. Median 5-year survival rates were 35% and 57% in patients with and without β symptom.

A statistically significant difference was not found between survival times of those with, and without splenic involvement (p=0.46). A statistically significant difference did not exist between patients receiving radiotherapy or any other treatment (p=0.55). Median survival times in patients receiving radiotherapy and other therapies were 48 and 72 months, respectively. Median 5-year survival rate of those receiving radiotherapy was 32 percent.

A statistically significant difference was found between patients with serum albumin levels below 3.5 g/dL and above (p<0,001). Median length of the survival time was 72, and 36 months in patients with albumin levels of ≥3.5 g/dL, and <3,5 g/dL, respectively. The patients with albumin levels of <3.5 g/dL had 4.66 times higher risk of mortality. Median 5-year survival rate of the patients with serum albumin levels of ≥3.5 g/dL was 59%.

A statistically significant difference was found between patients with and without LDH values of ≥380 U/L (p=0.01). Median survival times were 48, and 72 months for patients with LDH levels of ≥380 U/L and <380 U/L, respectively. Patients with LDH levels over 380 U/L had a 1.96 times higher risk of death relative to patients with LDH levels below 380 U/L. Median survival rate of the patients with LDH levels of ≥380 U/L was detected to be 39%.

A statistically significant difference was found as for median survival times between patients with ß2 microglobulin levels of ≥3000 ng/mL (72 months), and <3000 ng/mL (132 months, p=0.03). Patients with ß2 microglobulin levels of ≥3000 ng/mL had a 2.06 times higher mortality risk relative to patients with <3000 ng/mL. Median survival rate of the patients with microglobulin levels of <3000 ng/mL was estimated as 69%.

A statistically significant difference was not found between patients with serum uric acid levels of ≥5.7 and < 5.7 mg/dL regarding median survival times (60 vs 72 months) (p=0.95). Median 5-year survival rate in patients with serum uric acid levels below 5.7 mg/dL was 54%.

A statistically significantly difference in median survival times was found between patients with lymphocyte counts of ≥1500 mm^3 and < 1500 mm^3 (72 vs 36 months) (p=0.003). Patients with lymphocyte counts below 1500 mm3 had a 1.95 times higher risk of mortality relative to other group of patients. Median 5-year survival time was 56% in patients with lymphocyte counts ≥1500 mm^3.

A statistically significant difference was not found between patients with and without bone marrow involvement regarding median survival times (48 months for both groups (p=0.36). Median survival time in patients without bone marrow involvement was estimated as 45 percent.

A statistically significant difference was found between patients with and without extranodal involvement for overall survival rates (p=0.03). Median survival times for patients with and without extranodal involvement were 36, and 84 months, respectively. The patients with extranodal involvement had a 1.56 times higher risk of death. Median 5- year survival rate in patients without extranodal involvement was 56 percent. The patients were evaluated in stages 1-2, and 3-4. Survival times of stages 1-2, and 3-4 were statistically significantly different. (p=0.048). Median survival times in stages1-2, and 3-4 were 72, and 48 months, respectively. Stage 3-4 patients had a 1.53 times higher risk of death

versus stage1-2 patients. Median survival rates in stage 1-2 and 3-4 patients were 55, and 45%, respectively.

IPI scores of the patients were evaluated as 0 -1 (low), 2 (low-moderate), 3 (moderate-high), and 4-5 (high). A statistically significant difference was found between groups (p=0.001). Median survival times differed between IPI 0-1, vs 3; IPI 0-1 vs 4-5; IPI 2 vs 4-5. Median survival times of the patients were as follows: IPI 0-1, 96 months; IPI 2, 72 months, IPI 3, 48 months, and IPI 4-5, 36 months.

Discussion

In 1970s, and 1980s incidence of NHL, and related mortality rates demonstrated annual increase of 4 percent. From the year 1990 on, increase in the incidence rates of NHL decreased, however still an annual increase of 1-2% is detected. Although incidence of NHL increases in the whole world, incidence rates differ in diverse geographic regions, and vary with some etiological factors as environmental factors, and socioeconomic levels [6].

The American Cancer Society's most recent estimates for non-Hodgkin's lymphoma for 2016 are; about 72,580 people (40,170 males and 32,410 females) will be diagnosed with NHL. This includes both adults and children. About 20,150 people will die from this cancer [7].

Since NHL belongs to a very heterogeneous group of patients, determination of prognostic factors other than prognosis, and identification of patient groups with poor prognosis carry utmost importance [4].

Our study population mostly consisted of male patients. As seen in many other studies male/female (1.2 1/1) ratio represented male dominancy. Male dominancy rates differed among countries (USA, 1.43; Europe. 1.23: Austria, 1.52; Greece 1.16, and Korea, 1.6 [8-12].

Median age of our patients was 57 years (range, 16-87 years). Two studies performed in Turkey reported higher median ages of their patient population [2, 13]. However relative to Western society, median ages of our study and European estimates were similar [14, 15].

In our study incidence rates between genders as for mean age of its onset did not differ (women: 57±14.7 yrs, and men: 56±16.7 yrs). Based on literature data NHL is seen at an earlier age in men vs women. In all groups, incidence of NHL increases with age. After 55 years of age, increase in incidence becomes marked irrespective of the gender of the patients [16, 17].

In our study the most frequently (43.2%) histopathological subtype of NHL was diffuse large β–cell lymphoma (DLBCL), followed by follicular lymphoma (9.7%), and mantle cell lymphoma (7.5%). Similarly, in the literature the most frequently reported histological subtype was also DLBCL. Some data have indicated follicular subtype as the most frequently seen histological subtype [2, 18, 19]. In our study 9.7% of our patients had follicular lymphomas. Recent increase in the incidence of follicular lymphoma has been presumably attributed to the all-encompassing definition of this subtype.

When data of the studies performed in USA, Europe, and Asia, using Ann Arbor staging system, 45-54 % of NHL patients were at an advanced stage of their disease at the time of diagnosis [20-23]. In our study, 63.9% of our patients were at an advanced stage of their disease (stage 3-4) at the time of diagnosis which is higher than those reported in various literature studies.

Still different definitions have been made for primary nodal, and extranodal (PEL) lymphomas. In some of these definitions involvements of Waldeyer ring, spleen or bone marrow are considered as primary nodal disease, while in other publications they are considered as forms of extranodal involvements. In a study by Arican et al. from Turkey performed on 464 patients, the incidence of PEL was indicated as 25%, while in other studies from Turkey its incidence was determined to range between 25 and 46 percent. In Western countries its reported incidence varies between 24, and 48 percent [24, 25]. In a study performed by Di-Amore *et al.* [26] in Denmark, and Economopoules *et al.* [27] in Greece quite different incidence rates were reported (38 vs 45.6%). Such a wide spectrum of differences might stem from variations in the descriptions of primary extranodal lymphoma, and different geographic diversities. In our study extranodal involvement was detected in 43.9% of the cases, while in 56.1% the patients' nodal disease was found. Stomach was the most frequently seen site of extranodal involvement. Also as indicated in the literature, extranodal involvement was most frequently seen in the stomach in USA, and Asian countries. Followed by stomach, most frequently involvement of tonsils, small bowels, and skin has been reported [28-30]. In our study, lungs were the second most frequently involved organ. However, inclusion of

metastatic cases in this group might probably contribute to this higher incidence rates. Besides widespread use of PET in the diagnosis, and follow-up of lymphoma, might lead to misperception of pulmonary infections as cases of lymphoma which eventually contributed to erroneously higher rates of pulmonary involvement.

In our study we achieved complete (n=120; 62.5%), and partial response rates in 120, and 34 (17.7%) patients, respectively. More than an half (50.9%) of the patients survived. In a comprehensive meta-analysis of 2031 patients' complete response rate of 53 percent was reported [31].

According to 2007 data of a European study (EURO-CARE 4) 5-year survival rate was reported as 54.6 percent [32]. Based on data of SEER 13 study 5-year survival rate was reported as 69.1 percent [29]. In a study performed in Scandinavian countries between the years of 1964, and 2003, 5-year overall survival rate was reported to range between 50 and 60 percent [33]. In China average 5-year-survival rate was reported as 55.2 percent [30]. In our study, 5-year survival rate was 48.1 percent. This survival rate was lower than that of USA, and European survival rates, but at a similar level of China, and Scandinavian countries.

In an international organization (NHL Prognostic Factors Project) performed to develop a better prognostic model for NHL, 2031 patients with aggressive NHL were examined to formulate two indices namely IPI, and age adjusted IPI (sAAIPI). In this study age was detected to be a highly significant prognostic variable (>60, and ≤60 years) Seven factors were analysed, and only 5 of them were found to be significant including age, performance status, stage, number of extranodal involvements, and serum LDH levels [31, 34]. In our study complete response rates were detected in patients with IPI scores of 0 (n=17; 81%), 1 (n=38; 77.6%), 3 (n=23; 44.2%), 4 (n=10; 47.6%), and 5 (n=1; 33.3%). An inverse correlation was detected between IPI scores, and response rates. In the literature, higher IPI score, advanced stage, aggressive lymphoma subgroup according to WHO classification were observed to be poor prognostic parameters [31, 35].

In patients with NHL, various laboratory parameters have been analysed for their effects on treatment response, and overall survival rates. Prognostic values of sedimentation, and levels of LDH, CRP, albumin, uric acid, haemoglobin have been demonstrated in various studies [25, 36, 37]. In our study complete treatment response rates were achieved in indicated percentage of 80 patients with serum levels of LDH <380 U/L (70.3%), ß2 microglobulin <3000 ng/mL (83.3%), uric acid <5.7 mg/dL (72.5%), albumin lymphocyte count of ≥1500 mm3 (69.6%). In 97 patients with albumin levels of >3.5 g/dL complete response rate (74%) was achieved. In conclusion, similar to the literature, in our study prognostic values of the levels LDH, uric acid, ß2 microglobulin, albumin, and also lymphocyte counts have been also determined.

In our survival analysis, risk of mortality was higher in patients with β-symptom when compared with those without. A statistically significant difference existed between patients with and without β-symptoms. In patients who gave complete response to treatment a statistically significant difference was not detected as for the presence of β-symptom, however from clinical perspective, patients without β symptom had disease-free survival times longer than 36 months. In the literature, variable effects of the presence of β-symptom on the treatment response, and survival rates have been reported. In a study by Andrew *et al.* [38] presence of β-symptom was indicated as a prognostic factor which markedly effects survival time . In another study the effect of the presence of β-symptom on treatment response was not found, while its relationship with shorter survival time, and progression-free survival time was detected [14].

In the evaluation of overall survival, different from the literature data, a statistically significant difference was not found between survival times of the patients with affected bone marrow, spleen, and tonsils. In a study by Alici *et al.* [13] a statistically significant effect of bone marrow involvement on the treatment response, and survival rates was not detected.

In our study a statistically significant difference was found between patients with, and without extranodal involvement as for overall survival rates. A statistically significant difference was not detected between extranodal involvement, and disease-free survival. However, from clinical perspective, patients without extranodal involvement had 60-months longer survival time than those with nodal involvement. A significant difference has not been reported in the literature between patients with and without extranodal organ involvement [19, 30].

In studies performed after the year 2000, planning of the treatment has been recommended, and implemented based not only on the histology, and stage of the disease, but also on prognostic factors as

IPI. In especially high grade lymphomas individualization of the treatment is recommended based on IPI risk criteria [39]. Also in our study, IPI scores were graded as 0-1 (low risk), 2 (low-moderate risk), 3 (moderate-high risk), and 4-5 (high risk). Median survival times differed statistically significantly between IPI categories. In patients with complete response rates, median survival times did not differ between IPI categories.

In many studies performed unfavourable effects of higher serum LDH levels on treatment response, overall, and progression-free survival rates have been reported [34, 40]. In our study, patients with higher serum LDH levels had 2-times higher mortality risk. Overall survival rates were also significantly different.

Lower serum albumin levels have been associated with poor treatment response, and shorter survival times [34,40]. In our study a statistically significant difference was found between serum albumin levels, and overall survival rates. Patients with lower albumin levels had 4,5-fold higher mortality risk. However, a statistically significant difference was not found between albumin level, and disease-free survival. From clinical perspective, patients with higher albumin levels had a 48 month- longer disease-free life time.

In the literature lymphopenia has been demonstrated as a poor prognostic factor [41]. In our study lymphopenic patients had 2-fold higher mortality risk.

In recent years increases in β2 microglobulin value in parallel with NHL stage have been demonstrated, which indicate that it is an important and independent prognostic factor by itself or in combination with serum NHL value [42]. Similar to literature findings, in patients with increased β2 microglobulin values, 2-times higher risk of mortality was detected. In patients with higher β2 microglobulin values overall survival and disease-free survival times were shorter with a worse treatment response when compared with the healthy individuals.

Conclusions

Clinical characteristics, treatments applied, and their outcomes, survival rates, and the importance of prognostic factors which may be effective on the survival were retrospectively evaluated.

Mean age of our patients was 57±15.8 years. Our study population consisted of relatively greater number of male patients in compliance with the literature. Patients in the advanced stage of the disease were more numerous than indicated in the literature. IPI score, β symptom, levels of LDH, albumin, ß2 microglobulin, and lymphocyte counts had prognostic value. Risky patient groups regarding this issue should be followed up more closely. Stomach was the most frequently involved organ. Advanced stage, higher IPI score, and extranodal organ involvement were associated with shorter survival times. Our study findings were comparable with literature data.

Every day new developments have been observed in the diagnosis, classification, and treatment of NHL Therefore as an important issue, each centre should evaluate its own treatment outcomes, and prognostic factors effective on survival rates.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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