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THE PROGNOSTIC SIGNIFICANCE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO PATIENTS WITH LYMPHOMA

LENFOMA HASTALARINDA NÖTROFİL LENFOSİT ORANININ PROGNOSTİK ÖNEMİ

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ABSTRACT

Objective: The neutrophil-to-lymphocyte ratio (NLR) has been recently proposed as a simple, inexpensive prognostic factor in cancer patients. We aimed to investigate the prognostic meaning of pretreatment NLR in patients with lymphoma.

Material and Method: Patients aged over 18 years with lymphoma who were diagnosed, followed-up and treated between January 2011 and December 2017 in the department of internal medicine were enrolled in this study. The data of 82 patients (62 NHL and 20 HL) were obtained retrospectively. The relationship between the NLR and baseline characteristics, laboratory parameters, prognosis, and survival outcome were evaluated.

Results: In patients with HL, the older age group of the patients at the time of diagnosis had a high mortality rate and pleural effusion had a significant negative effect on OS (p=0.008, p=0.035). In patients with NHL, an advanced age, high IPI score, decreased PLT level and elevated beta 2 microglobulin were associated with a high mortality rate (p=0.001, p=0.044, p=0.023, p=0.009).

Conclusion: A relation between the NLR and mortality and OS could be not demonstrated in HL patients and NHL patients. The retrospective analysis with a small sample size, late-diagnosed patients population and single-centre study may be the causes of these unexpected results.

Keywords: Hodgkin lymphoma, Non-hodgkin lymphoma, Neutrophil/lymphocyte ratio, Prognosis

ÖZET

Amaç: Sistemik inflamasyon göstergesi olan nötrofil-lenfosit oranı (NLR), kanser hastalarında son zamanlarda önerilen basit ve ucuz bir prognostik faktördür. Çalışmamızda, tedavi öncesi yüksek NLR değerinin lenfoma hastalarında kötü sağkalımı gösterdiği hipotezine dayanarak lenfoma hastalarında tedavi öncesi NLR değerlerinin geriye dönük prognostik anlamını inceledik.

Gereç ve Yöntem: Çalışmamıza Ocak 2011 ve Aralık 2017 tarihleri arasında İstanbul Tıp Fakültesi iç hastalıkları ve geriatri bölümünde tanı konulan, takip ve tedavi edilmiş 18 yaş üstü lenfoma tanılı hastalar dahil edildi. Sekseniki hastanın verileri retrospektif olarak hastane otomasyon sistemlerinden elde edildi. NLR ve temel karakteristikleri laboratuar parametreleri, prognoz ve sağkalım sonuçları arasındaki ilişki değerlendirildi.

Bulgular: HL hastalarında, tanı anında daha ileri yaş grubundaki hastalarda yüksek mortalite hızı ve plevral efüzyonun varlığı uzun dönem sağkalım üzerine anlamlı negatif etkiye sahipti (p=0,008, p=0,035). NHL hastalarında, ileri yaş yüksek IPI skoru, düşük PLT seviyesi ve yüksek beta 2 mikroglobulin düzeyi yüksek mortalite oranıyla ilişkili bulundu (p=0,001, p=0,044, p=0,023, p=0,009).

Sonuç: HL ve NHL hastalarında NLR ile mortalite ve uzun dönem sağkalım arasında bir ilişki gösterilememiştir. Bu retrospektif analizin küçük bir örneklem büyüklüğüne sahip olması, geç tanı konulmuş hasta popülasyonu ve tek merkezli bir çalışma olması bu beklenmedik sonucun nedeni olabilir.

Anahtar Kelimeler: Hodgkin lenfoma, Non-hodgkin lenfoma, Nötrofil/Lenfosit oranı, Prognoz

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INTRODUCTION

Lymphomas are clonal neoplasms characterised by the enlargement of abnormal lymphoid cells that may develop in any organ but usually include lymph nodes (1). Lymphomas are broadly classified as Hodgkin lymphomas (HLs) and non-Hodgkin lymphomas (NHLs) (2). Scoring systems such as IPI for NHL and IPS-7 for HL are most commonly used to estimate the prognosis at the time of diagnosis. These models identified several risk factors for the prediction of survival including age, gender; the serum level of lactate dehydrogenase (LDH), albumin, hemoglobin, leukocytes, and lymphocytes; ECOG (Eastern Cooperative Oncology Group) performance status, Ann Arbor stage, and the number of extra-nodal involvement site (3). In addition, genetic markers, new molecular gene expression profiling, immunohistochemistry -based detection of prognostic biomarkers and positron emission tomography have been investigated as potential predictive technologies. However, these parameters sometimes may be inefficient in determining the prognosis in daily practice (4). Therefore, other prognostic biomarkers for lymphoma, which are widely available, inexpensive, and easily interpreted, are needed for clinicians. In recent years, tumour microenvironment, host immunity and host inflammation response have been identified as an important driver of cancer progression in different types of cancer. NLR at diagnosis has been shown as a new independent prognostic factor in patients with HL and some NHL-subtypes and a significant correlation between NLR and the accepted prognostic markers for lymphoma has been determined (4-6). The aim of this study was to evaluate the possible relationship between NLR and clinical parameters, prognosis and survival in lymphoma patients.

MATERIAL AND METHOD

Study objectives

In recent years, some studies have demonstrated that the NLR to be an easily available and inexpensive marker that can be used to predict the prognosis of lymphoma, but there are yet no sufficient and conclusive results to explain the direct effect of the NLR level on the survival of lymphoma patients and on the clinicopathological parameters of the tumour (4-6). Thus, this study aimed to evaluate the prognostic significance of the NLR in patients with lymphoma.

Study design

Study population

Male and female patients aged from 17 to 101 years with lymphoma who were diagnosed, followed-up and treated between January 2011 and December 2017 in the department of internal and geriatrics medicine at the Istanbul Faculty of Medicine were enrolled in this study.

Inclusion and exclusion criteria

Male or female patients older than 18 years with a definitive diagnosis of HL and NHL in the department of internal and geriatrics medicine at the Istanbul Faculty of Medicine were included in the study. Patients without a sufficient medical record and regular follow-ups have not been considered for this study.

Methods

In this study, 82 patients with lymphoma were enrolled through a retrospective review of the patients' records. A total of 82 patients were eligible, including 20 HL and 62 NHL patients. A retrospective chart review was conducted to obtain demographic data regarding the patients, including pathological diagnostic subtype, age at diagnosis, gender, disease staging, presence of bone marrow involvement and presence of organomegaly, life status and the overall survival (OS) of patients. Through the same method we were also provided with CBC at diagnosis including haemoglobin (Hb), red cell distribution width (RDW), white blood count (WBC), neutrophil and lymphocyte counts, platelet count (PC), serum beta-2 microglobulin (ß2M), LDH, calcium, albumin levels, erythrocyte sedimentation rate, C-reactive protein (CRP) and imaging findings.

Statistical considerations and data analysis

All anonymised data obtained were entered into a computerised database created with Microsoft Excel 2013 and NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used in data analysis. The suitability of the quantitative data for normal distribution was tested with the Shapiro-Wilk test and graphical analysis. Student t test was used to compare between two groups of quantitative variables that showed normal distribution; the Mann-Whitney U test for comparison between two groups of quantitative variables that did not show normal distribution. The Pearson chi-square test, Fisher-Freeman-Halton test and Fisher's Exact test were used to compare the qualitative data. OS was analysed using Kaplan– Meier curves. Comparisons of survival between the different groups were made using the log- rank test. The significance level was assumed to be p=0.05. For visualisation of the collected data and the resulting prevalence values and relationships, pie charts, bar charts, and tables were used.

Data management

All necessary steps have been taken in the planning and administration of this pilot study to ensure that the collected data is reliable, accurate and consistent according to the Good clinical practice-guidelines. The Ethics Commission of the Istanbul Faculty of Medicine of Istanbul University has approved the study (Date: 20.12.2018, Number: 1743). All patients were coded with a consecutive number and pseudonymised for further evaluation.

Only authorised persons have access to the original data. All the patients were 18 years old or over at the time of participation.

Risk-benefit assessment

The included patients had no direct benefit from the study. The only possible risk of disclosure of sensitive patient data was minimised by the pseudonymisation and access restriction.

RESULTS

Statistics analysis

A total of 82 (100%) patients with 20 (24.4%) HL and 62 (75.6%) NHL were included in the pilot study. Of the HL patients, 11 (55%) were male and 9 (45%) were female. There were 41 (66.1%) male and 21 (33.9%) female patients diagnosed with NHL. When the diagnoses of cases were evaluated according to pathological subtypes; 31 (50.0%) of patients with NHL were DLBCL (Diffuse Large B-Cell Lymphoma) subtype, followed by FL (Follicular Lymphoma) with 8 (13.0%) patients. Five (38.4%) of patients with HL were of the nodular sclerosing type HL subtype; 3 (23.1%) patients had mixed cellular type HL. While the mean age of the individuals with HL was 47.25±20.27 (17-82) years, the mean age of the individuals with NHL was 55.1±16.67 (19-101) years. Clinically, at the time of diagnosis, 2 patients (3.3%) were identified as stage I, 6 patients (10%) as stage II, 15 patients (25%) as stage III, and 37 patients (61.7%) as stage IV on the basis of the Ann Arbor staging system in the NHL patients. A total of 8 (13.3%) patients were in the early stage and 52 (86.7%) patients were diagnosed at the advanced stage among the NHL patients. When the NHL patients were evaluated according to an IPI score, at the time of diagnosis, 17.74% of patients were in the low risk group, 77.42% of patients in the intermediate risk group and 4.84% of patients in the high risk group. It has been seen that 53.2% (n=33) of patients are still alive. The median and mean survival times of patients were analysed. The follow-up period ranged from 18 to 106 months and the median survival was 16.9±20.7 months. In the whole blood count, the mean ESR was 53.2±40.3 (4-127) mm\h, the mean CRP was 50.38±55.13 (0-203) mg\l, the mean LDH was 567.2±440.8 (108-1735) U/L, the mean NLR was 4±3.1 (0.1-13.2), the mean PLT was 256916.1±192712.2 (22600-900000) µL and the mean beta 2 microglobulin was 6.44±3.75 (1.7-11.94). Based on the laboratory reference range, ESR was detected as high in 40 (64.5%) patients, CRP in 46 (75.4%) patients, LDH levels in 42 (71.2%) patients, beta 2 microglobulin in 18 (85.7%) patients and PLT was found as low in 17 (27.4%) patients.

When the diagnoses of cases in the HL patients were evaluated according to pathological subtypes; the distribution of subtype were 38.4% (n=5) nodular sclerosis, 23.1% (n=3) mixed cellularity, 21.3% (n=3) lymphocyte-rich and 15.4% (n=2) lymphocyte-depleted. Clinically, at the time of diagnosis, 2 patients (12.5%) were identified as stage I, 4 patients (25.0%) as stage II, 5 patients (31.25%) as stage III, and 5 patients (31.25%) as stage IV on the basis of the Ann Arbor staging system. A total of 6 (37.5%) patients were in the early stage and 10 (62.5%) patients were diagnosed at the advanced stage. When the HL patients were evaluated according to the IPS score, at the time of diagnosis, 25% of patients were in the low risk group, 68.75% of patients in the intermediate risk group and 6.25% of patients in the high risk group. It has been seen that 70.0% (n=14) of patients are still alive. The median and mean survival times of patients were analysed. The follow-up period ranged from 31 to 111 months and the median survival was 90±83.6 months. In the whole blood count, the mean ESR was 83.3±38.9 (13-142) mm\h, the mean CRP was 119.7±78.6 (10-273) mg\l, the mean LDH was 409.7±151.6 (241-764) U/L, the mean NLR was 5.56±2.94 (2,21-13,2), the mean PLT was 353943.8±193320.9 (32100-669000) µL. Based on the laboratory reference range, ESR was detected high in 13 (76.5%) patients, CRP in 15 (100%) patients, LDH levels in 17 (94.4%) patients, and PLT in 9 (56.2%) patients.

The demographics assessment of NHL patients by mortality are shown in Table 1.

The demographics assessment of HL patients by mortality are shown in Table 2.

When the relationship between mortality and clinical parameters were analysed in patients with NHL, there was a statistically significant relationship between age and mortality ($p=0.001$; $p<0.01$). The mean age was 62.44±16.9 (28-101) years in dead patients and 48.60±13.71 (19-68) years in patients who were still alive; the ages of the dead NHL patients at diagnosis were higher compared to the patients who were still alive. There was a statistically significant relationship between the IPI score and mortality ($p=0.044$, $p<0.05$). The frequency of a high-risk group was higher in dead patients compared to patients who were still alive. No significant correlation was found between gender, disease stage, pleural effusion, bone marrow infiltration, extranodal involvement and mortality. ($p=0.950$, $p=0.742$, $p=0.783$, $p=0.380$, $p=0.783$, respectively). When the relationship between mortality and laboratory parameters were analysed in patients with NHL, there was a statistically significant relationship between PLT, beta 2 microglobulin measurements and mortality ($p=0.023$, $p<0.05$; $p=0.009$, $p<0.05$). No significant correlation was found between the ESR level, the CRP level, the LDH level, the NLR and mortality. ($p=0.654$, $p=0.094$, $p=0.732$, $p=0.930$, respectively).

The mean PLT was 191972.41±122345.15 (30000-534000) µL in dead patients and 313987.87±224757.18 (22600-

Table 1: Demographics of NHL patients by mortality.

Non-Hodgkin Lymphoma (n=62)		Mortality		
		Alive (n=33)	Death (n=29)	p values
Age	*Min-Max (Median)*	19-68 (50)	28-101 (63)	[a]***0.001***
	Mean±SD	48.60±13.71	62.44±16.9	
Gender	*Female*	12 (57.1)	9 (42.9)	[b]***0.950***
	Male	21 (51.2)	20 (48.8)	
Staging (n=60)	*Staging I*	2 (100)	0 (0)	[c]***0.742***
	Staging II	3 (50.0)	3 (50.0)	
	Staging III	7 (46.7)	8 (53.3)	
	Staging IV	21 (56.8)	16 (43.2)	
Pleural effusion	*No*	27 (55.1)	22 (44.9)	[b]***0.783***
	Yes	6 (46.2)	7 (53.8)	
Bone marrow infiltration	*No*	17 (58.6)	12 (41.4)	[b]***0.380***
	Yes	16 (50.0)	16 (50.0)	
Extranodal involvement	*No*	7 (50.0)	7 (50.0)	[b]***0.783***
	Yes	26 (54.2)	22 (45.8)	
IPI score	*Low risk*	8 (80.0)	2 (20.0)	[c]***0.044****
	Intermediate risk	25 (51.0)	24 (49.0)	
	High risk	0(0)	3(100)	
PLT	*Min-Max (Median)*	22600-900000 (245400)	30000-534000 (165000)	[d]***0.023****
	Mean±SD	313987.87±224757.18	191972.41±122345.15	
NLR	*Min-Max (Median)*	0.2-11 (2.81)	0.1-13.2 (2.9)	[d]***0.930***
	Mean±SD	3.92±3.05	3.91±3.30	
Beta2 microglobulin	*Min-Max (Median)*	1.67-12 (2.94)	4.6-13.6 (9.62)	[d]***0.009****
	Mean±SD	4.39±3.1	8.7±3.2	
LDH	*Min-Max (Median)*	163-1735 (403.5)	108-1520 (408)	[d]***0.732***
	Mean±SD	562.15±412.52	574.77±472.41	
ESR	*Min-Max (Median)*	4-120 (41)	5-127 (39)	[d]***0.654***
	Mean±SD	55.45±41.50	50.68±39.57	
CRP	*Min-Max (Median)*	0-189 (18)	1-203 (45.5)	[d]***0.094***
	Mean±SD	40.52±52.94	60.61±56.43	

[a]*Student t Test,* [b]*Pearson Chi-Square Test* [c]*Fisher Freeman Halton Test,* [d]*Mann Whitney U Test. *p<0.05 **p<0.01*

900000) µL in patients who were still alive; the PLT levels of the dead NHL patients were found to be lower than those for the patients who were still alive (Figure 1).

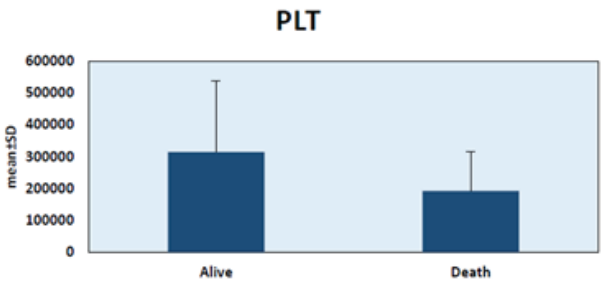

Figure 1: The PLT distributions of NHL patients by mortality.

The mean beta 2 microglobulin was 8.7±3.2 (4.6-13.6) mg/dl in dead patients and 4.39±3.1 (1.67-12) mg /dl in patients who were still alive, the beta 2 microglobulin levels of the dead NHL patients were higher than those for the patients who were still alive (Figure 2).

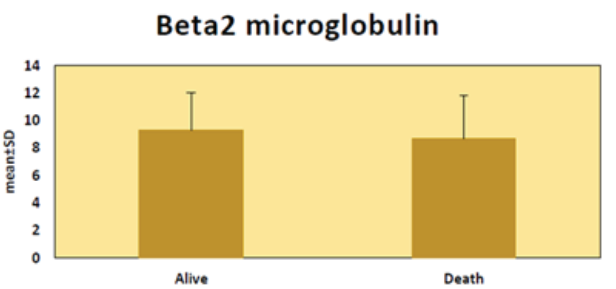

Figure 2: The beta 2 microglobulin distrubutions of NHL patients by mortality.

Table 2: Demographics of HL patients by mortality.

Hodgkin Lymphoma (n=20)		Mortality		
		Alive (n=13)	Death (n=7)	p values
Age	*Min-Max (Median)*	17-82 (32)	39-80 (67)	[a]***0.008****
	Mean±SD	38.92±17.98	62.71±15.01	
Gender	*Female*	6 (66.7)	3 (33.3)	[e]***1.000***
	Male	7 (63.6)	4 (36.4)	
Staging (n=16)	*Staging I*	2 (100)	0 (0)	[c]***1.000***
	Staging II	3 (75.0)	1 (25.0)	
	Staging III	3 (60.0)	2 (40.0)	
	Staging IV	3 (60.0)	2 (40.0)	
IPS score (n=16)	*Low risk*	3 (75.0)	1 (25.0)	[c]***0.471***
	Intermediate risk	8 (72.73)	3 (27.27)	
	High risk	0 (0)	1 (100)	
Pleural effusion	*No*	12 (70.6)	5 (29.4)	[b]***0.783***
	Yes	1 (33.3)	2 (66.7)	
Bone marrow infiltration	*No*	10 (62.5)	6 (37.5)	[e]***1.000***
	Yes	3 (75.0)	1 (25.0)	
Extranodal involvement	*No*	6 (66.7)	3 (33.3)	[e]***1.000***
	Yes	7 (63.6)	4 (36.4)	
PLT	*Min-Max (Median)*	32100-669000 (400000)	114000-615000 (463000)	[d]***0.692***
	Mean±SD	344554.55±194304.46	374600.00±212102.10	
NLR	*Min-Max (Median)*	2.6-17.5 (6.3)	2.6-20.9 (6.1)	[d]***0.777***
	Mean±SD	7.08±4.57	7.80±7.52	
LDH	*Min-Max (Median)*	241-764 (352)	276-674 (361.5)	[d]***1.000***
	Mean±SD	411.17±162.73	406.83±141.17	
ESR	*Min-Max (Median)*	13-142 (95)	64-122 (90)	[d]***0.752***
	Mean±SD	79.92±44.30	91.60±23.13	
CRP	*Min-Max (Median)*	10.9-218 (124)	13-667 (196.5)	[d]***0.228***
	Mean±SD	116.40 65.84	233.72±234.19	

[a]*Student t Test,* [b]*Pearson Chi-Square Test,* [c]*Fisher Freeman Halton Test,* [d]*Mann Whitney U Test* [e]*Fisher's Exact Test. *p<0.01*

When the relationship between mortality and clinical parameters was analysed in patients with HL, there was a statistically significant relationship between age and mortality (p=0.008; p<0.01). The mean age was 62.71±15.01 (39-80) years in death patients and 38.92±17.98 (17-82) years in patients who were still alive; the ages of the dead HL patients at diagnosis were found to be higher than those of the patients who were still alive. No significant correlation was found between gender, disease stage, IPS score, pleural effusion, bone marrow infiltration, extranodal involvement, and mortality (p=1.000, p=1.000, p=0.471, p=0.783, p=1.000, p=1.000, respectively).

When the relationship between mortality and laboratory parameters were analysed in patients with HL, no significant correlation was found between the PLT level, the ESR level, the CRP level, the LDH level, the NLR and mortality (p=0.692, p=0.752, p=0.228, p=1.000, p=0.777, respectively).

When the relationship between OS and clinical parameters was analysed in patients with NHL; the OS rate was significantly higher in the 60 years and younger age group at the time of diagnosis (p=0.008, p<0.05) and the patients in the high risk group (high IPI score) had a worse survival rate (p=0.016, p<0.05) (Figure 3 and Figure 4).

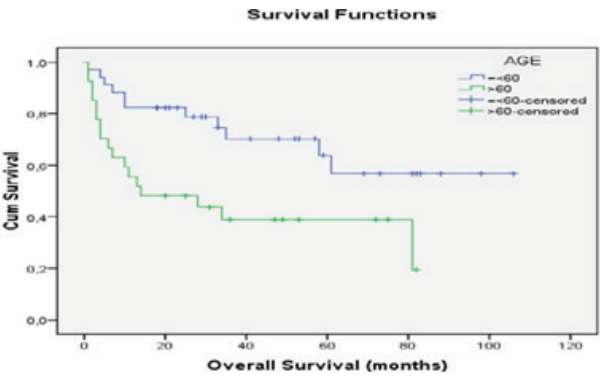

Figure 3: Survival rate correlation with age in NHL population.

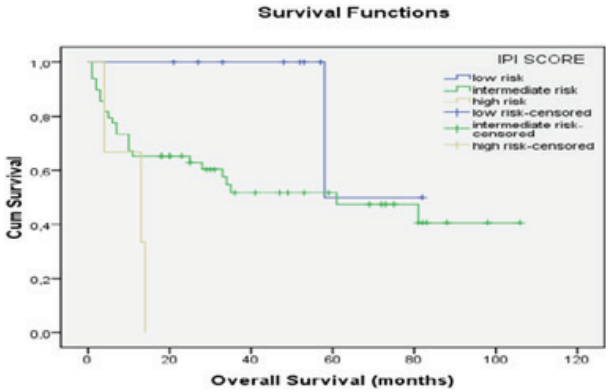

Figure 4: Survival rate correlation with IPI score in NHL population.

When the relationship between OS and laboratory parameters was analysed in patients with NHL; the decreased PLT level had a significantly negative effect on OS (p=0.017, p<0.05) (Figure 5).

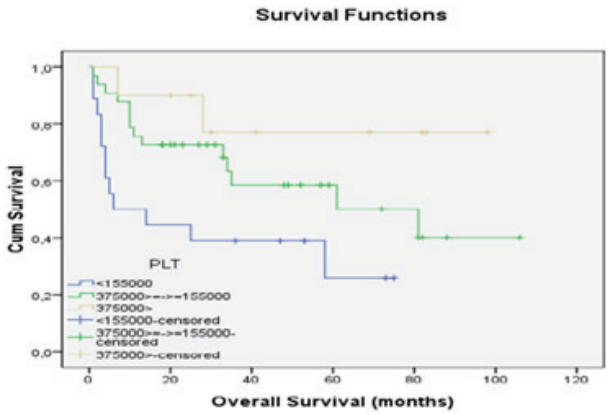

Figure 5: Survival rate correlation with PLT level in NHL population.

When the relationship between OS and clinical parameters was analysed in patients with HL, the presence of pleural effusion at the time of diagnosis indicated a poor survival (p=0.035, p<0.05) (Figure 6).

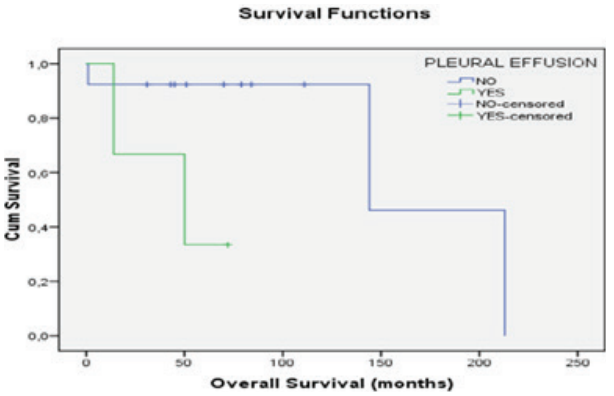

Figure 6: Survival rate correlation with pleural effusion in HL population.

DISCUSSION

Lymphomas are lymphoproliferative neoplasms that may originate from different stages of development of immune system cells. Lymphomas are broadly divided as HLs and NHLs, based on the differences these two groups show in their morphologic features, clinical manifestations, prognosis, proportion of neoplastic cells and treatment (2).

The relationship between the factors that may have a prognostic significance in lymphoma, and mortality and overall survival was investigated in our study. Older age indicates poor prognosis in many studies (9, 11, 4, 17). In our study, there was a statistically significant relationship between age and mortality in patients with HL and in patients with NHL. When patients were evaluated as over 60 and under 60 years old in two groups, it was found that older age in patients with NHL has an unfavourable impact on OS but had no effect on OS in patients with HL. No statistically significant effect of gender on prognosis and overall survival in lymphoma was reported in previous studies (9, 11, 4, 18). In our study, as consistent with the relevant literature, no significant correlation was found between gender and mortality and OS in patients with HL and in patients with NHL. Previous studies predicted a worse outcome in Stage III-IV patients defined as advanced stage according to the Ann Arbor staging system (9, 4, 12, 15, 17). No significant correlation was found between the disease stage and mortality and OS in patients with HL and in patients with NHL in our study. This may be because the study was performed at a single centre and the patients may have been diagnosed at an advanced stage. However, in the literature; as in our study, there are studies in which there is no relationship between disease stage and survival (11, 14, 16). Several studies have shown that high IPI and IPS scores indicate a poor survival (13, 15, 19, 20). In our study, there was a statistically significant correlation between the IPI score and mortality in patients with NHL and the NHL patients with a high IPI score had a shorter survival rate, but no significant correlation was found between the IPS score and mortality and OS in patients with HL.

In our study, no significant correlation was found between pleural effusion and mortality and OS in patients with NHL, but HL patients with pleural effusions were found to have a poor survival rate.

In the last studies, it was found that the decreased PLT level predicts a worse prognosis in lymphoma patients (10, 21, 22). In our study, there was a statistically significant relationship between the PLT level and mortality in patients with NHL and our study showed that the low PLT level in NHL patients indicates a worse survival rate, but no significant correlation was found between the PLT level and mortality and OS in patients with HL.

The NLR is being investigated lately as a new biomarker to predict prognosis in lymphomas. In reported results, the NLR was related to an unfavourable survival rate (4, 14, 5, 23). In our study, no significant correlation was found between the NLR and mortality and OS in patients with HL and in patients with NHL. A relation between a high LDH level and worse outcome for lymphoma has very often been demonstrated (8, 4, 13, 18, 24). No significant correlation was found between the LDH level and mortality and OS in patients with HL and in patients with NHL in our study.

However, as in our study, there was no relationship between the LDH level and survival in some studies (12, 15, 16). Serum beta 2 microglobulin level is an established prognostic factor that has been proven to have an adverse effect on survival (7, 20, 25). In our study, as similar to the literature, there was a statistically significant correlation between beta 2 microglobulin and mortality.

CONCLUSION

In this study, the relationship between clinical and laboratory parameters of patients diagnosed with lymphoma, and mortality and OS was retrospectively analysed. In conclusion, a relation between NLR, mortality and OS could be not demonstrated in HL patients and NHL patients in our study. The retrospective analysis with a small sample size, a late-diagnosed patients population and single-centre study may be the causes of these unexpected results. More extensive studies on this subject are needed to investigate this non-invasive, simple, and potential prognostic marker in cases of lymphoma.

Ethics Committee Approval: This study was approved by the Ethical Committee of the Istanbul University Istanbul Faculty of Medicine. (Date: 20.12.2018, No: 1743)

Informed Consent: Written consent was obtained from the participants.

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