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Evaluation of Clinical Features, Treatment Approaches and Treatment Outcomes of Children with Non-Hodgkin Lymphoma

Hodgkin Dışı Lenfomalı Çocukların Klinik Özelliklerinin, Tedavi Yaklaşımlarının ve Tedavi Sonuçlarının Değerlendirilmesi

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Abstract

Aim: To evaluate the demographic and clinical characteristics, treatment approaches and outcomes of our pediatric patients with non-Hodgkin lymphoma diagnosed and treated in our center.

Material and Method: Between 2006 and 2022, the oncologic charts of the patients diagnosed and followed up as non-Hodgkin lymphoma were reviewed retrospectively.

Results: Eighty children with non-Hodgkin lymphoma were included in this study. There were 55 boys (68.8%) and 25 girls (31.2%). The patients' ages ranged from 2 to 18 years (median: 11.1 years). Nine patients (11.3%) had primary immunodeficiency. Sixty-three of the patients were stage III (78.7%). The majority pathologic subtype was Burkitt lymphoma (n: 31, 38.8%). The overall survival and event-free survival rates were 71.7% and 71.5%, respectively. The patients' overall survival rates without and with primary immunodeficiency was 81.1% and 11.1%, respectively. There was a significant difference between these two groups. Cox regression analysis showed that advanced stage and concomitant primary immunodeficiency have been risk factors for prognosis.

Conclusion: Intensive treatment approaches have increased overall survival rates in children with non-Hodgkin lymphoma. However, this success rate cannot be achieved in non-Hodgkin lymphoma children with primary immunodeficiency.

Keywords: Child, non-Hodgkin lymphoma, prognosis

Öz

Amaç: Klinimizde, non-Hodgkin lenfoma tanısı konulan ve tedavi edilen çocuk hastalarımızın demografik ve klinik özelliklerini, tedavi yaklaşımlarını ve sonuçlarını değerlendirmektir.

Gereç ve Yöntem: 2006-2022 yılları arasında non-Hodgkin lenfoma tanısı alan ve takip edilen hastaların onkolojik dosyaları geriye dönük olarak incelendi.

Bulgular: Bu çalışmaya Hodgkin dışı lenfomalı seksen çocuk dahil edildi. Elli beş erkek (%68,8) ve 25 kız (%31,2) vardı. Hastaların yaşları 2 ile 18 yıl arasında değişmekteydi (ortanca: 11,1 yıl). Dokuz hastada (%11,3) primer immün yetmezlik vardı. Hastaların 63'ü evre III (%78,7) idi. Çoğunluk patolojik alt tip Burkitt lenfoma idi (n: 31, %38,8). Genel sağkalım ve olaysız sağkalım oranları sırasıyla %71,7 ve %71,5 idi. Primer immün yetmezliği olmayan ve olan hastaların genel sağkalım oranları sırasıyla %81,1 ve %11,1 idi. Bu iki grup arasında anlamlı bir fark vardı. Cox regresyon analizi, ileri evre ve eşlik eden primer immün yetmezliğin prognoz için risk faktörleri olduğunu göstermiştir.

Sonuç: Yoğun tedavi yaklaşımları, Hodgkin olmayan lenfoma olan çocuklarda genel sağkalım oranlarını artırmıştır. Ancak primer immün yetmezliği olan non-Hodgkin lenfoma çocuklarında bu başarı oranı elde edilememektedir.

Anahtar Kelimeler: Çocuk, non-Hodgkin lenfoma, prognoz

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) accounts for approximately 6-8% of all childhood malignant diseases. However, it accounts for approximately 50% of all childhood malignant diseases in equatorial Africa. In children, there are two main features that distinguish NHLs from adults, these are extranodal presentation and the histopathological type. NHL subtypes seen in childhood are usually high grade, and four main groups are frequently observed, which are T- or B- lymphoblastic lymphoma (LBL), Burkitt lymphoma (BL), diffuse large B cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL).[1] Although the etiology of NHL is exactly unknown, exposure to drugs and/or radiation, congenital or acquired immunodeficiency, and some viral infections, especially Epstein-Barr virus, are important risk factors.[1]

Currently, the main treatment for childhood NHLs is the treatment of oncological emergency, if any and chemotherapy. The chemotherapy regimen that can be preferred is related to the histopathological type. Generally, "Berlin-Frankfurt-Munster" (BFM) protocols or "Lymphomes Malins B" (LMB) protocols in BL or DLBCL; BFM, BFM like or "Lymphomes Malins B" (LMT) protocols in lymphoblastic lymphoma; and CHOP or BFM-NHL90 protocols in ALCL are used. The role of surgical treatment or radiotherapy in childhood NHL is very limited.[1,2] Important prognostic factors well-known to date are histopathological subtype, disease burden, extent of disease, stage, minimal disseminated disease, minimal residual disease, some cytogenetics and some molecular genetics.[1-3] The outcomes of childhood NLS have improved dramatically in last years. The survival rates have reached >90%.[1]

Herein, we aimed to evaluate the demographic and clinical characteristics, treatment approaches and outcomes of our pediatric patients with non-Hodgkin lymphoma diagnosed and treated in our center.

MATERIAL AND METHOD

Ethical approval was obtained from the local ethics committee of Selçuk University for this study (No: 2022/193, Date: Apr 12, 2022). From 2006 to 2022, the oncologic charts of the patients diagnosed and followed up as NHL were reviewed retrospectively. Patients with missing information on their oncology charts or those who did not come for follow-up were excluded from the study. Eighty patients with NHL were included in this study.

Demographic features of the patients, including age, gender and ethnicity, was recorded. At the time of diagnosis, the patients' symptoms, physical examination findings, complete blood count, lactate dehydrogenase levels, pathological diagnoses, stages, treatments and follow-up periods were recorded.

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR) were calculated in these complete blood count. In the complete blood count at the time of admission, hemoglobin level, leukocyte count, neutrophil, lymphocyte, monocytes and platelet counts were obtained at the time of admission. Within the laboratory findings, leukocytes, neutrophils, lymphocytes, monocytes, eosinophil counts, and hemoglobin levels were grouped according to the lower and upper limit values for that age group.[4] Cut-off values for NLR, PLR, and MLR were 3.17, 180, and 0.29, respectively.[5]

Modified BFM-95 (from 2006 to 2019) and LMB-89 chemotherapy (since 2020) regimens for Burkitt lymphoma and DLBCL; modified BFM chemotherapy regimen for LBL; and modified BFM-90 chemotherapy regimen for ALCL were used.[6-8] In patients with CNS negative, the dose of methotrexate was reduced to 3 gr/m² in AA and BB courses in the modified BFM-95 protocol. If CNS involvement was present, the dose of methotrexate was administered as 5 gr/m². Similarly, in BFM protocols used for LBL, the doses of methotrexate in Protocol M were reduced from 5 gr/m² to 3 gr/m². In the BFM-90 protocol used for ALCL, the methotrexate doses in AA and BB courses were also applied as 3 gr/m². Radiotherapy was administered for CNS-positive patients and one primary mediastinal large B-cell lymphoma.

Statistical Analysis

IBM SPSS-21 (Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad, San Diego, USA) were used for statistical analysis. As descriptive statistics: Frequency and percentage values for categorical variables; For continuous variables, mean ± standard deviation were used if the distribution was normal, and median and minimum-maximum values were used if the distribution was not normal. In comparison of categorical data, chi-square or Fischer Exact test was used depending on whether it met the necessary assumptions. Because the distributions of the variables were not normal, the Mann-Whitney U test was used to compare the continuous variables of the two groups, and the Kruskal-Wallis test was used to compare the continuous variables of more than two groups. Bonferroni correction was performed when statistical significance was detected in the Kruskal Wallis test. Kaplan Meier survival analysis for all survival analysis, log-rank test for univariate analysis, and Cox-regression analysis for multivariate analysis were used. If the p value was less than 0.05, it was considered statistically significant.

RESULTS

During this period, 80 children with NHL were included in this study. Demographic and clinical characteristics of the patients are given in **Table 1**. There were 55 boys (68.8%) and 25 girls (31.2%). The patients' ages ranged from 2 to 18 years (median: 11.1 years). While 74 of them (92.5%) were Turks, six of them (7.5%) were refugees.

Table 1: The patients' demographic and clinical features

Demografic Features	N, (%)
Age, median, (minimum-maximum)	11.1 years (2-18)
Gender	
Male, n,(%)	55, (68.8%)
Female, n,(%)	25, (31.2%)
Clinical Features	
Co-morbity	
Primary immunodeficiency	9, (11.3%)
Nijmegen breakage syndrome	4
Ataxia telangiectasia	2
Common variable immunodeficiency	1
F-BAR domain only protein 1 (FCHO1) deficiency	1
Autism spectrum disorder	1
Localization	
Abdomen	25, (31.3%)
Mediastinum	25, (31.3%)
Nodal	17, (21.3%)
Head and neck	6, (7.5%)
Extranodal	6, (7.5%)
Disseminated	1, (1.3%)
Stage	
I	5, (6.2%)
II	3, (3.8%)
III	63, (78.7%)
IV	6, (7.5%)
Unknown	3, (3.8%)
Pathologic subtypes	
Burkitt lymphoma	31, (38.7%)
Diffuse large B-cell non-Hodgkin lymphoma	10, (12.5)
Lymphoblastic lymphoma	19, (23.8%)
Anaplastic large cell lymphoma	6, (7.5%)
Others	14, (17.5%)
Nodal marginal zone lymphoma	3, (3.8%)
Primary mediastinal large B-cell lymphoma	2, (2.3%)
Gray zone lymphoma	2, (2.3%)
T-cell rich large B-cell lymphoma	1, (1.3%)
Hepatosplenic T-cell lymphoma	1, (1.3%)
Peripheral T-cell lymphoma	1, (1.3%)
Pediatric-type follicular lymphoma	1, (1.3%)
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	1, (1.3%)
Polymorphic B-cell lymphoproliferative disorder	1, (1.3%)
Unclassifiable	1, (1.3%)

Nine patients (11.3%) had primary immunodeficiency. The duration of the symptom ranged from 1 day to 9 months (median, 1 month). The longest duration of symptoms was in the patient with nodal marginal zone lymphoma. The most common localizations were abdomen (n: 25, 31.3%) and mediastinum (n: 25, 31.3%). Sixty-three of the patients were stage III (78.7%). The patients with low stage including stages I and II were patients with low-grade NHL. Pathologic subtypes were Burkitt lymphoma (n: 31, 38.8%), DLCBL (n: 12.5%), LBL (n: 19, 23.8%), ALCL (n: 6, 7.5%) and others (n: 1417.5%). The most common rare NHL types are nodal marginal zone lymphoma (n: 3, 3.8%), primary mediastinal large B-cell lymphoma (n: 2, 2.3%) and gray zone lymphoma (n: 2, 2.3%). Interestingly, the other type called NHL, a very rare subtype for childhood, had primary immunodeficiency in five (38.5%) patients with the disease. Only four (6%) of the common NHL subtypes in children had primary immunodeficiency. The Fisher Exact test showed that this difference was statistically significant (p=0.005).

Hematological Parameters

The all NHL patients' lymphocyte counts ranged between 490/mm³ and 17200/mm³ with median 2045/mm³. Twenty-four patients (30%) had lymphopenia. The NLR of the all patients were between 0.5 and 600 (median, 2.21). The NLR was ≤ 3.17 in 49 patients (61.3%). The all patients' NLR values ranged from 17.44 to 1000 (median, 163.37). The PLR was ≤ 180 in 45 patients (56.3%). The MLR of the patients were between 0.002 and 4.31 (median, 0.31). The MLR of the patients were between 0.002 and 4.31 (median, 0.31) and the MLR was ≤0.29 in 39 patients (48.8%). The lymphocyte counts, NLRs, PLRs and MLRs of the patients according to the stage, pathologic subgroup, presence of primary immune deficiency, lactate dehydrogenase level, whether the event has developed or not, and outcomes are in **Table 2**.

Survival Analysis

Twenty of the patients died. Among our causes of death, in addition to progressive diseases, four patients had Stevens-Johnson syndrome and/or toxic epidermal necrolysis.[9] In addition, another reason that increased the mortality rate was the presence of NHL patients who developed in patients with primary immunodeficiency. The follow-up period of the patients ranged from two months to 16 years (median 5.8 years). The Kaplan-Meier estimated indicated that the rates overall survival and event-free survival for 80 patients given were 71.7% and 71.5%, respectively (**Figure 1A**).

Univariate Analysis

Table 3 shows the factors affecting the overall survival with the log-rank test (Mantel-Cox test). The Kaplan-Meier estimated indicated that the survival rate for 71 patients without primary immunodeficiency was 81.1% and for the patients with primary immune deficiency was 11.1% (**Figure 1B**). The Mantel-Cox test indicated that there was a significant difference between these two groups (X2 (1)=26.608, p < 0.0001). The Mantel-Cox test did not show the effect of other factors on overall survival.

Multivariate Analysis

Cox regression analysis was performed separately for lymphocyte count, NLR, PLR and MLR, as they were affected by each other. These analyses are in **Table 4**. Cox regression analysis showed that advanced stage and concomitant primary immunodeficiency have been risk factors for prognosis.

DISCUSSION

While childhood lymphomas are the third most common malignant disease in developed countries, it is the second most common malignant disease in developing countries. Both Hodgkin lymphomas and NHLs in children have attracted the attention of many researchers and still do. Although the etiology of NHL is not exactly known, immunodeficiency (congenital or acquired), viral infections (Epstein Barr virus, human immune deficiency virus, human T-lymphotropic virus), some drugs (anti-cancer drugs or immunosuppressive drugs) and radiotherapy are known etiological factors.[1-3] There are two different important factors that distinguish childhood NHL from adult lymphoma. These are the histopathological type and the more frequent extranodal involvement. Another important feature is that the survival rates are generally excellent with intensive chemotherapy protocols.[1-3]

In children, the most common pathological subgroups are BL, LBL (T- or B-), DLBCL, and ALCL. Some subgroups such as pediatric marjinal zone lymphoma, pediatric-type follicular lymphoma and mucosa-associated lymphoid tissue lymphoma are very rare NHL subgroups in childhood.[1-3] In our study, the main NHL subgroups were BL, DLBCL, and LBL. The rare NHL subgroups for children such as nodal marginal zone lymphoma, primary mediastinal large B-cell lymphoma, gray zone lymphoma were determined. Interestingly, we observed that these subgroups, which are rare in childhood, are more common in children with primary immunodeficiency. The high number of NHLs in patients with primary immunodeficiency in our center can be explained by the presence of two comprehensive pediatric immunology centers in our city.

In children, survival rates have been near excellent (85 to over 90%) with intensive chemotherapy regimens and supportive care over the last few decades.[1] Important prognostic factors well-known to date are histopathological subtype, disease burden, extent of disease, stage, minimal disseminated disease, minimal residual disease, some cytogenetics and some molecular genetics.[1-3] Survival rates vary according to pathological subgroups. For example, in studies of the same group, it was reported as 90.8% for BL, 78.8% for ALCL and 65.1% for DLCBL.[10-12] For the 80 patients included in our study, the overall survival and event-free survival rates were 71.7% and 71.5%, respectively, with a median follow-up time of 5.8 years. Twenty of the patients died. Among our causes of death, in addition to progressive diseases, four patients had Stevens-Johnson syndrome and/or toxic epidermal necrolysis.[9]

Table 2. The patients' lymphocyte counts, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and monocyte-to-lymphocyte ratio according to subgroups

	Lymphocyte counts (/mm³)		Neutrophil-to-lymphocyte ratio		Platelet-to-lymphocyte ratio		Monocyte-to-lymphocyte ratio	
	Median, (min-max)	p values	Median, (min-max)	p values	Median, (min-max)	p values	Median, (min-max)	p values
Stage		0.160		0.045[a]		0.006[b]		0.036[c]
Stage I + II, (n: 10, 12.5%)	2790, (1290-4650)		1.62, (0.72-3.46)		114.55, (80.22-153.5)		0.23, (0.14-0.67)	
Stage III, (n: 64, 80%)	2000, (490-6000)		2.45, (0.59-600)		202.37, (26.67-1000.0)		0.34, (0.002-4.31)	
Stage IV, (n: 6, 7.5%)	1905, (1100-17200)		1.86, (0.5-4.55)		101.51, (17.44-490.91)		0.21, (0.08-0.75)	
Pathologic subgroups		0.448		0.485		0.518		0.408
Burkitt lymphoma, (n: 31, 38.7%)	2400, (600-6000)		2.17, (0.59-600)		185.02, (38.71-657.0)		0.28, (0.002-1.45)	
DLBCL, (n: 10, 12.5%)	1820, (544-4650)		3.24, (0.75-17)		125.16, (83.8-657.0)		0.33, (0.18-1.17)	
LBL, (n: 19, 23.8%)	2100, (760-17200)		1.78, (0.5-8.68)		177.13, (17.44-490.91)		0.26, (0.05-0.93)	
ALCL, (n: 6, 7.5%)	1710, (970-3640)		6.04, (1.42-15.28)		297.72, (81.59-522.68)		0.52, (0.27-0.89)	
Others, (n: 14, 17.5%)	1950, (490-2800)		1.94, (0.65-30.9)		138.69, (26.88-1000.0)		0.29, (0.14-4.31)	
Co-morbid disease		0.223		0.415		0.183		0.508
Without PID, (n: 71, 88.7%)	2070, (490-17200)		2.25, (0.5-600)		174.76, (17.44-1000.0)		0.29, (0.002-1.45)	
With PID, (n: 9, 11.3%)	1900, (490-4100)		1.78, (0.65-30.9)		128.31, (38.78-918.37)		0.36, (0.17-4.31)	
Lactate dehydrogenase level		0.252		0.441		0.365		0.200
Normal, (n: 15, 18.8%)	2740, (970-4100)		1.78, (0.75-15.28)		134.0, (38.78-522.68)		0.25, (0.15-0.89)	
High, (n: 65, 81.2%)	1920, (490-17200)		2.33, (0.5-600)		164.85, (17.44-1000)		0.34, (0.002-4.31)	
Hemoglobin levels		0.814		0.077		0.544		0.566
Normal, (n: 59, 73.8%)	2060, (490-17200)		1.94, (0.65-600)		153.5, (17.44-1000.0)		0.29, (0.05-1.45)	
Anemia, (n: 21, 26.2%)	2030, (490-6000)		3.3, (0.65-600)		223.32, (38.71-918.37)		0.34, (0.002-4.31)	
Event		0.025		0.739		0.441		0.016
Not developed, (n: 59, 73.8%)	2300, (490-17200)		2.25, (0.5-600)		153.5, (17.44-1000.0)		0.27, (0.002-1.33)	
Developed, (n: 21, 26.2%)	1650, (490-4140)		1.94, (0.59-30.9)		178.7, (26.88-918.37)		0.39, (0.2-4.31)	
Outcome		0.032		0.938		0.498		0.018
Alive, (n: 60)	2285, (490-17200)		2.29, (0.5-600)		158.0, (17.44-1000.0)		0.28, (0.002-1.33)	
Dead, (n: 20)	1710, (490-4140)		1.93, (0.59-30.9)		171.47, (26.88-918.37)		0.39, (0.2-4.31)	

DLBCL: diffuse large B-cell lymphoma, LBL: lymphoblastic lymphoma, ALCL: anaplastic large cell lymphoma, PID: primary immune deficiency; a Stage I+II vs Stage III, p=0.048 (This is the p-value after Bonferroni correction.) b Stage I+II vs Stage III, p=0.009 (This is the p-value after Bonferroni correction.); c Stage I+II vs Stage III, p=0.041 (The p value after Bonferroni correction is 0.123).

Table 3: Univariate analysis of the all patients with non-Hodgkin lymphoma.

	Estimated overall survival (%)	Standard error (%)	Log rank test (Mantel Cox)		
			χ2	df	p-value
Gender			2.614	1	0.106
Male	76	6.5			
Female	63.1	9.8			
Disease			1.180	1	0.277
Local (Stage I and II)	88.9	10.5			
Advanced disease (Stage III and IV)	69.5	6			
Pathological subtypes			8.862	4	0.065
Burkitt lymphoma, (n: 31)	81.8	7.5			
DLBCL, (n: 10)	90	9.5			
LBL, (n: 19)	76.5	10.3			
ALCL, (n: 6)	44.4	22.2			
Others	42.3	15			
Co-morbid disease			26.608	1	<0.0001
Without PID, (n: 71)	81.1	5			
With PID, (n: 9)	11.1	10.5			
Lactate dehydrogenase level, (N: 120-300 U/L)			1.392	1	0.238
Normal, (n: 15)	85.1	9.7			
High, (n: 65)	68.7	6.3			
Leukocyte counts ǂ			0.015	1	0.903
Normal, (n: 49)	74.9	6.7			
High, (n: 27)	72.2	10			
*Low, (n: 4)	25	21.7			
Hemoglobin ǂ			3.417	1	0.065
Normal, (n: 59)	79.3	5.6			
Anemia, (n: 21)	54.9	11.3			
Platelet counts, (N: 150,000-450,000/mm³)			0.177	1	0.674
Normal, (n: 53)	70.5	7.1			
High, (n: 23)	77.5	8.9			
*Low, (n: 4)	50	25			
Neutrophil counts ǂ			0.097	1	0.756
Normal, (n: 61)	76.1	5.9			
High, (n: 16)	70.7	12.6			
*Low, (n: 3)	0	0			
Lymphocyte counts ǂ			1.206	1	0.272
Normal, (n: 55)	75.2	6.4			
*High, (n: 1)	Not available	Not available			
Low, (n: 24)	63	10.5			
Neutrophil-to-lymphocyte ratio §			0.035	1	0.852
≤ 3.17, (n: 49)	71.2	7.2			
> 3.17, (n: 31)	72.2	8.5			
Platelet-to-lymphocyte ratio §			0.02	1	0.888
≤ 180, (n: 45)	70.4	7.9			
> 180, (n: 35)	72.8	7.8			
Monocyte-to-lymphocyte ratio §			3.032	1	0.082
≤ 0.29, (n: 39)	81	7.3			
> 0.29, (n: 41)	63.7	7.8			

DLBCL: diffuse large B-cell lymphoma, LBL: lymphoblastic lymphoma, ALCL: anaplastic large cell lymphoma, PID: primary immune deficiency, *They were not included in the analysis. ǂ The normal values were determined according to age (4). § The cutoff values were taken from the study by Tezol et al (5).

Table 4: Multivariate analysis of the all patients with non-Hodgkin lymphoma.

	B	SE	Wald	df	p-value	Exp(B)
Analysis with lymphocyte count						
Burkitt lymphoma			10.353	4	0.035	
Diffuse large B cell lymphoma	0.817	0.973	0.705	1	0.401	2.264
Lymphoblastic lymphoma	0.349	1.336	0.068	1	0.794	1.417
Anaplastic large cell lymphoma	-1.736	0.919	3.570	1	0.059	0.176
Others	2.000	1.106	3.268	1	0.071	7.389
Gender (male/female)	-0.864	0.558	2.403	1	0.121	0.421
Co-morbidity (without/with PIY)	-3.171	0.907	12.211	1	<0.0001	0.042
Stage I + II			15.349	2	<0.0001	
Stage III	-5.484	1.530	12.837	1	<0.0001	0.004
Stage IV	-3.265	0.930	12.339	1	<0.0001	0.038
Lactate dehydrogenase levels (normal/high)	-1.855	0.959	3.740	1	0.053	0.156
Hemoglobin levels (normal/anemia)	0.645	0.536	1.450	1	0.229	1.907
Lymphocyte counts (normal/low)	-0.482	0.529	0.830	1	0.362	0.618
Analysis with neutrophil to lymphocyte ratio						
Burkitt lymphoma			9.756	4	0.045	
Diffuse large B cell lymphoma	0.702	0.983	0.511	1	0.475	2.018
Lymphoblastic lymphoma	0.298	1.414	0.044	1	0.833	1.347
Anaplastic large cell lymphoma	-1.512	0.883	2.935	1	0.087	0.220
Others	2.016	1.161	3.014	1	0.083	7.510
Gender (male/female)	-0.752	0.539	1.946	1	0.163	0.471
Co-morbidity (without/with PIY)	-3.163	0.943	11.244	1	0.001	0.042
Stage I + II			14.760	2	0.001	
Stage III	-5.387	1.527	12.448	1	<0.0001	0.005
Stage IV	-3.107	0.910	11.671	1	0.001	0.045
Lactate dehydrogenase levels (normal/high)	-1.989	1.000	3.958	1	0.047	0.137
Hemoglobin levels (normal/anemia)	0.643	0.548	1.380	1	0.954	0.969
Neutrophil to lymphocyte ratio	-0.031	0.541	0.003	1	0.954	0.969
Analysis with platelet to lymphocyte ratio						
Burkitt lymphoma			9.871	4	0.043	
Diffuse large B cell lymphoma	0.703	0.984	0.511	1	0.475	2.020
Lymphoblastic lymphoma	0.312	1.387	0.051	1	0.822	1.367
Anaplastic large cell lymphoma	-1.518	0.907	2.802	1	0.094	0.219
Others	2.026	1.147	3.118	1	0.077	7.582
Gender (male/female)	-0.752	0.539	1.944	1	0.163	0.471
Co-morbidity (without/with PIY)	-3.162	0.947	11.148	1	0.001	0.042
Stage I + II			14.617	2	0.001	
Stage III	-5.394	1.525	12.519	1	<0.0001	0.005
Stage IV	-3.117	0.936	11.092	1	0.001	0.044
Lactate dehydrogenase levels (normal/high)	-1.997	0.995	4.026	1	0.045	0.136
Hemoglobin levels (normal/anemia)	0.638	0.539	1.404	1	0.236	1.893
Platelet to lymphocyte ratio	-0.014	0.542	0.001	1	0.980	0.986
Analysis with monocyte to lymphocyte ratio						
Burkitt lymphoma			7.942	4	0.094	
Diffuse large B cell lymphoma	0.879	1.006	0763	1	0.382	2.407
Lymphoblastic lymphoma	0.056	1.398	0.002	1	0.968	1.058
Anaplastic large cell lymphoma	-1.376	0.862	2.549	1	0.110	0.253
Others	1.800	1.166	2.385	1	0.123	6.049
Gender (male/female)	-0.861	0.567	2.311	1	0.128	0.423
Co-morbidity (without/with PIY)	-3.047	0.963	10.007	1	0.002	0.047
Stage I + II			15.334	2	<0.0001	
Stage III	-5.085	1.511	11.332	1	0.001	0.006
Stage IV	-3.423	0.955	12.839	1	<0.001	0.033
Lactate dehydrogenase levels (normal/high)	-1.715	1.016	2.850	1	0.091	0.180
Hemoglobin levels (normal/anemia)	0.491	0.539	0.832	1	0.362	1.634
Monocyte to lymphocyte ratio	-0.944	0.668	1.998	1	0.157	0.389

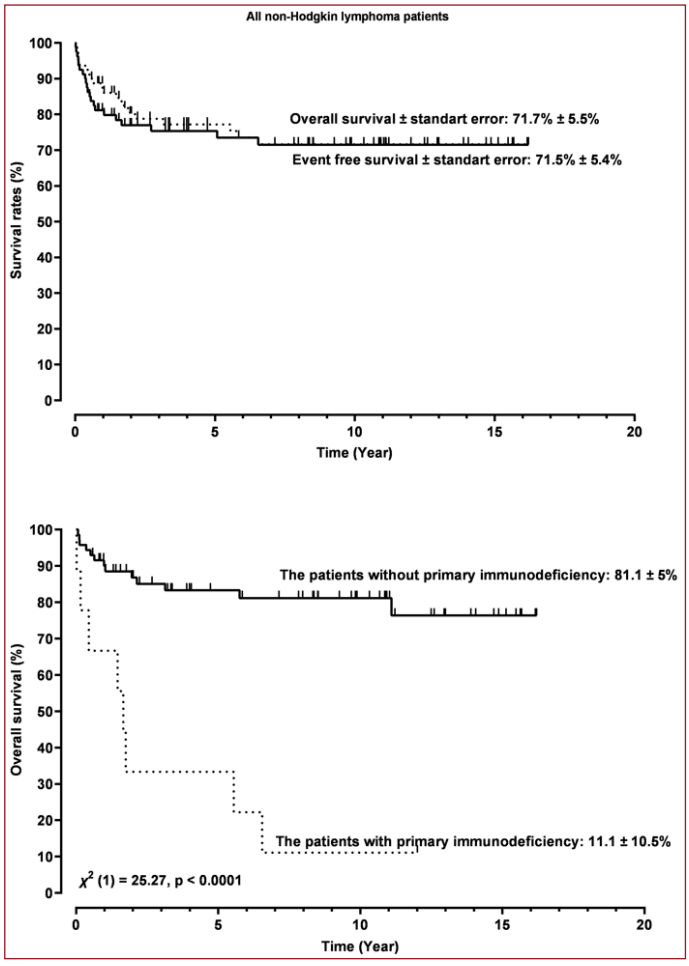

Figure 3. Correlation between FSS score and left median sense NCV in CTS patients

In addition, another reason that increased the mortality rate was the presence of NHL patients who developed in patients with primary immunodeficiency. That is, the overall survival rate was 81.1% in NHL patients without primary immunodeficiency, while this rate was 11.1% in NHL patients with primary immunodeficiency. The difference was statistically quite significant. In the univariate analysis, when the factors affecting the overall survival analysis were examined, we could not show the effect of any of the prognostic factors we emphasized above. This situation can be explained by the small number of our patients. However, in the cox regression analysis explained how it was done in the material method section by us, we determined that the presence of primary immunodeficiency and stage affect the prognosis.

The relationship of both Hodgkin lymphoma and non-Hodgkin lymphoma with the immune system and immune deficiencies attracts the attention of many researchers. Recently, there are studies on the use of some biomarkers such as NLR, PLR, MLR in lymphomas.[5,13,14] Biological markers such as NLR, PLR, and MLR were found to be higher in children with lymphoma compared to children with reactive lymphadenopathy. In multivariate odd ratios of variables for predicting malignancy in all children, the statistical significance of age, extension, hemoglobin and MLR were determined. However, this study did not differentiate between Hodgkin lymphoma and NHL.[5] In a study in children with Hodgkin lymphoma, NLR was associated with high disease burden and B symptoms.[13] In another study conducted in children with Hodgkin lymphoma, lymphocyte counts, NLR, and PLR may be useful markers for determining the outcomes in children with Hodgkin lymphoma was determined. In our study, a relationship was found between stage and NLR, PLR and MLR. This relationship was found to be statistically different between stage I+II and stage III. It was observed that NLR, PLR and MLR increased with stage. Logically, it was expected to increase further at stage IV, but a decrease was found. This can be explained by the low number of patients in stage IV. While the lymphocyte count was lower in the patients who developed the event and the patients who died, the MLR values were higher. These parameters may be helpful in predicting the prognosis. However, it should not be forgotten that more patients are needed.

Study limitation

The significant limitation in this study is the small number of patients in some subgroups.

CONCLUSION

The excellent survival rates are obtained with intensive treatment approaches and supportive treatments in childhood NHLs. Similarly, NHL development rates in this patient group increase with the increase in survival rates with both initial and supportive treatments in patients with primary immunodeficiency. There is a need to develop new treatment strategies in the group of patients with primary immunodeficiency who develop NHL.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission for this study was obtained from Selcuk University Faculty of Medicine, Local Ethics Committee with the number 2022/193 dated 12.04.2022.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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