Impact on the survival of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and monocyte-lymphocyte ratio on prognosis in children with Hodgkin lymphoma

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ABSTRACT

الأهداف: تقييم الفائدة السريرية لعدد العدلات المطلق الموصوف حديثًا إلى نسبة عدد الخلايا الليمفاوية المطلقة (NLR)، وعدد الصفائح الدموية المطلقه إلى نسبة تعداد الخلايا الليمفاوية المطلقة (PLR)، وتعداد الخلايا الوحيدة المطلقة إلى نسبة تعداد الخلايا الليمفاوية المطلقة (MLR) على تشخيص الأطفال المصابون بسرطان الغدد الليمفاوية هودجكين (HL).

المنهجية: أجرينا تقييم للخصائص السريرية بأثر رجعي، والخصائص المخبريه (تعداد الخلايا الليمفاوية، PLR، NLR، و MLR)، والعلاج، ونتائج 52 طفلاً مصابًا بمرض HL في قسم أمراض الدم والأورام لدى الأطفال، جامعة سلجوق، قونية، تركيا، خلال الفترة من يناير 2006م حتى ديسمبر 2021م.

النتائج: اشتمل مرضى الدراسة على 27 (51.9%) أناث و25 (48.1%) ذكور. تراوحت أعمارهم بين 3-17.5 عام (الوسيط=9 سنوات). كان هناك 22 مريضا في المرحلة الثانية، و24 في المرحلة الثالثة، و6 في المرحلة الرابعة. كانت المجموعة الفرعية المرضية النسيجية الأكثر انتشارًا هي النوع المصلب العقدي (53.8%). كان معدل البقاء على قيد الحياة 5 سنوات 93.7%. اختلف معدل البقاء الإجمالي بناء على عدد الخلايا الليمفاوية (p<0.0001)، و NLR (p=0.018)، و PLR (p=0.009). ومع ذلك، لم تكن أي من العوامل الإنذارية في التحليل الأحادي المتغير من عوامل الخطر النذير (p>0.05) في التحليل متعدد المتغيرات.

الخلاصة: أعداد الخلايا الليمفاوية، و NLR، و PLR علامات مهمه لتحديد النتائج عند الأطفال المصابين بمرض HL.

Objectives: To evaluate the clinical utility of the recently described absolute neutrophil counts to absolute lymphocyte counts ratio (NLR), absolute platelet counts to absolute lymphocyte counts ratio (PLR), and absolute monocyte counts to absolute lymphocyte counts ratio (MLR) on prognosis in children with Hodgkin lymphoma (HL).

Methods: We retrospectively evaluated the clinical characteristics, laboratory features (lymphocyte counts, NLR, PLR, and MLR), treatment, and results of 52 children with HL in the Department of Pediatric Hematology and Oncology, Selcuk University, konya, Turkey, from January 2006 until December 2021.

Results: The patients included 27 (51.9%) females and 25 (48.1%) males. The age of the patients ranged between 3-17.5 years old (median: 9 years). There were 22 patients in stage II, 24 in stage III, and 6 in stage IV. The most prevalent histopathological subgroup was the nodular sclerosing type (53.8%). The 5-year overall survival rate was 93.7%. The overall survival rate differed based on lymphocyte counts (p<0.0001), NLR (p=0.018), and PLR (p=0.009). However, none of the prognostic factors in the univariate analysis were not prognostic risk factors (p>0.05) in the multivariate analysis.

Conclusion: Lymphocyte counts, NLR, and PLR may be useful markers for determining the outcomes in children with HL.

Keywords: child, Hodgkin lymphoma, lymphocyte counts, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, prognosis

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Hodgkin lymphoma (HL) has been a curable malignant disease since the last century. The main objectives in HL are to improve the outcome of the high-risk group, similar to those of the low- and intermediate-risk groups, and to minimize treatment-related toxicities.[1] The well-known factors affecting the outcome in HL are stage, the presence of B symptoms, the presence of bulky disease, extra-nodal involvement, increased number of tumor sites, male gender, high erythrocyte sedimentation rate, anemia, and leukocytosis.[2-5]

The role of the immune system and its cells in the occurrence, development, course, and prognosis of malignant diseases has been known for several years and continues to attract attention. Another point in malignant disease, well known, is inflammation in the tumor tissue. The cells that play significant roles in both the immune and inflammatory response to malignant disease are specifically lymphocytes and neutrophils. Recently, some systemic inflammatory markers obtained from lymphocytes, neutrophils, monocytes, and platelets have been employed in various disease groups. These markers include absolute neutrophil counts to absolute lymphocyte counts ratio (NLR), absolute platelet counts to absolute lymphocyte counts ratio (PLR), and absolute monocyte counts to absolute lymphocyte counts ratio (MLR) and so on.[6-18] However, there are few reports on the use of these markers in childhood malignant diseases. Furthermore, several studies have highlighted its effects on prognosis in children with malignant diseases.[6,11-18] In a study carried out on children with reactive lymphadenopathy and children with lymphoma, the lymphoma group's NLR, PLR, and MLR values of children with lymphoma were higher than the reactive lymphadenopathy group.[6] In another study carried out on children with HL, they discovered that NLR was associated with tumor burden and B symptoms.[18]

This study evaluated the clinical utility of recently described NLR, PLR, and MLR on prognosis in children with HL.

Methods. From January 2006 until December 2021, we retrospectively examined 53 children with HL. Demographic and clinical features, laboratory findings, pathological diagnoses, treatment approaches (such as chemotherapy regimens and radiotherapy), and outcomes were obtained from their oncologic charts. We excluded a patient with nodular lymphocyte-predominant HL from this study. Thus, this study enrolled 52 patients diagnosed with classical HL. Patients' age was grouped as ≤5 years, 5-10 years, and ≥10 years old. Ethical approval was obtained from Selcuk University, Faculty of Medicine Ethics Board, Konya, Turkey (2021/437). Also, the Declaration of Helsinki and principles of Good Clinical Practice was complied in this study.

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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.[19] The high erythrocyte sedimentation rate was defined as greater than twice the laboratory upper limit of normal (>40 mm/h). Similarly, elevated lactate dehydrogenase was defined as more than twice the upper limit of normal. The NLR, PLR, and MLR were calculated from complete blood counts at the time of diagnosis. Cut-off value for NLR was 3.17, 180 for PLR, and 0.29 for MLR.[6]

Furthermore, we evaluated the patients using physical examination, laboratory and imaging studies (such as neck and abdominal ultrasounds; neck, chest, and abdominal computed tomography) and positron emission tomography-computed tomography (after 2010). The definitive diagnosis was made by pathological examination. Bone marrow biopsy was carried out except for stage IA and IIA patients.

Ann Arbor staging system was used. The patients were divided into 3 groups as low- (non-bulky stage IA or IIA disease), intermediate- (stage IB or IIB disease without bulk; bulky stage IA or bulky stage IIA disease; stage IIAE and stage IIIA, regardless of bulk), and high-risk groups (stage IIB with bulk, stage IIIB, or stage IV disease).

During this period, ABVD chemotherapy regimen containing adriamycin, bleomycin, vinblastine, and dacarbazine ± COPP chemotherapy regimen containing cyclophosphamide, vincristine, prokabazine and prednisone; or OPPA containing vinristine, prednisone, procarbazine, and adriamycin for female patients; OEPA containing vinristine, prednisone, etoposide, and adriamycin for male patients ± the COPP protocol were used in our institute according to drug supply variations.

Since 2015, the COPDac chemotherapy regimen containing cyclophosphamide, vincristine, prednisone, and dacarbazine has been used instead of COPP. Involved field radiotherapy was preferred.

Statistical analysis. Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA) was used. Frequency and percentage values were used for categorical data. If the numerical data distribution is normal, the mean ± standard deviation (SD) was given, if it is not normal, the median (mdn) value (minimum-maximum values) was given. We estimated the overall survival rates using Kaplan-Meier analysis, and the prognostic factors' effect survival differences were compared using the Mantel-Cox test (log-rank test). Then, we carried out the multivariate analysis by Cox

Table 1 - The patients' demographic and clinical features.

Variables	n (%)
Age, median year (minimum - maximum)	9 year (3-17.5)
Age groups	
≤5 years old	11 (21.2)
5-10 years old	17 (32.7)
≥10 years old	24 (46.1)
Gender	
Male	25 (48.1)
Female	27 (51.9)
Nationality	
Turkish	50 (96.2)
Refugee	2 (3.8)
Symptom duration, median months (minimum - maximum)	1 month (1-24)
Symptoms	
Lymphadenopathy	52 (100)
Fever	16 (30.8)
Weight loss	13 (25.0)
Night sweats	10 (19.2)
Pruritus	4 (7.7)
B symptoms	22 (42.3)
Other clinical features	
Bulk disease involvements	10 (19.2)
Splenic	14 (26.9)
Bone	5 (9.6)
Pulmonary	4 (7.7)
Bone marrow	2 (3.8)
Liver	1 (1.9)
Stage	
I	0 (0.0)
II	22 (42.3)
III	24 (46.2)
IV	6 (11.5)
Risk group	
Low	15 (28.8)
Intermediate	16 (30.8)
High	21 (40.4)
Histologic variant	
Classical Hodgkin lymphoma	
Nodular sclerosis type	28 (53.8)
Mixed cellularity type	18 (34.7)
Lymphocyte rich type	1 (1.9)
Lymphocyte depleted type	0 (0.0)
Unclassified	5 (9.6)
Chemotherapy regimens	
Adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD)	17 (32.7)
Oncovin, prednisone, procarbazine hydrochloride, and adriamycin (OPPA) or OEPA + COPP	14 (26.9)
OPPA or oncovin, etoposide phosphate, prednisone, and adriamycin (OEPA)	7 (13.5)
ABVD + cyclophosphamide, oncovin, procarbazine hydrochloride, and prednisone (COPP)	7 (13.5)
ABVD + cyclophosphamide, oncovin, prednisone, and dacarbazine (COPDac)	6 (11.5)
Adriamycin, bleomycin sulfate, vincristine sulfate, etoposide, prednisone, and cyclophosphamide	1 (1.9)

Values are presented as a number and (%).

regression method. A *p*-value of <0.05 was considered significant.

Results. This study included 52 pediatric patients with pathologically proven classical HL. The demographic and clinical characteristics of the patients are shown in Table 1. A total of 50 patients were Turkish, while 2 were refugees from Syria, 27 (51.9%) patients were female, and 25 (48.1%) were male. The patients' age ranged from 3-17.5 years old (Mdn: 9 years). Nearly half (46.1%) were ≥10 years old.

There were 22 patients in stage II, 24 in stage III, and 6 patients in stage IV Also, the low-risk group included 15 patients, the intermediate-risk groups included 16 patients, and the high-risk group included 21 patients. The most prevalent histopathological subgroup was the nodular sclerosing type (53.8%).

Table 2 - The patients' hematological parameters.

Parameters	n (%)
*Hemoglobin levels, gr/dL, median (min-max)**	11.8 (7.1-14.2)
Normal	33 (63.5)
Anemia	19 (36.5)
*Leukocyte counts, mm³, median (min-max)**	9805 (3860-23260)
Normal	37 (71.2)
High	11 (21.2)
Low	4 (7.6)
Neutrophil counts, mm³, mean±SD	7230.8±4535.7
Normal	31 (59.6)
High	20 (38.5)
Low	1 (1.9)
Lymphocyte counts,mm³, mean±SD	2319.1±1040.4
Normal	44 (84.6)
Low	8 (15.4)
Monocyte counts, mm³, mean±SD	718.7±341.2
Normal	32 (61.5)
High	17 (32.7)
Low	3 (5.8)
Platelets counts, mm³, mean±SD	381326.9±133083.3
Normal	40 (76.9)
High	11 (21.2)
Low	1 (1.9)
*NLR, median (min-max)**	2.78 (0.46-56.5)
≤3.17	29 (55.8)
>3.17	23 (44.2)
*PLR, median (min-max)**	156.3 (9.96-2235.0)
≤180	31 (59.6)
>180	21 (40.4)
*MLR, median (min-max)**	0.3 (0.05-2.5)
≤0.29	22 (44.2)
>0.29	30 (55.8)

*The distributions of these parameters were not normal. Values are presented as a number and (%). NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, gr/dL: grams/decilitre, min: minimum, max: maximum, SD: standard deviation

Tables 2 & 3 show the hematological and inflammatory markers of the patients. We detected anemia in 19 (36.5%) patients, leukocytosis in 11 (21.2%) patients, leukopenia in 4 (7.6%) patients, neutrophilia in 20 (38.5%) patients, neutropenia in one (1.9%) patient, lymphopenia in 8 (15.4%) patients, and thrombocytopenia in one (1.9%)patient.

Neutrophil-to-lymphocyte ratio of all patients ranged from 0.46-56.5 (mdn: 2.78). The NLR of 29 patients were ≤3.17 and 23 patients had NLR >3.17.

The mdn PLR value was 156.3 (range: 9.96-2235.0). A total of 31 patients had PLR ≤180 and 21 patients had PLR >180. The patients' MLR values ranged from 0.05-2.5 (mdn: 0.3). There were 22 patients with MLR ≤0.29 and 30 patients with MLR >0.29.

Survival analyses. The whole patients' follow-up time ranged from 4 months until 15.7 years old, (median, 8.3 years). A total of 4 (7.5%) patients died with progressive disease. The 5-year overall survival rates as 93.7%. Table 4 shows the patients' survival analyses according to subgroups. The overall survival rate differed based on lymphocyte counts (p<0.0001), NLR (p=0.018), and PLR (p=0.009). However, by Cox regression analysis, it was revealed that tumor lymphocyte counts, NLR, and PLR, which are all prognostic factors in univariate analysis, were not prognostic risk factors (p>0.05).

Discussion. Hodgkin lymphoma, originating from lymphocytes, is a malignant disease that has attracted a lot of attention from many researchers for many years and continues to attract attention. Recently, improvements in the treatment outcomes of HL, especially a decrease in long-term side effects, have been achieved with risk- and response-based treatment approaches. Early response to treatment (favorable prognostic factor); pre-treatment factors, including advanced stage (stage III and IV), the presence of B symptoms, the presence of bulky disease, extra-nodal extension, male gender, the presence of high erythrocyte sedimentation rate, anemia, high leukocyte counts, and some serum markers are well known prognostic factors in HL.[2-5] This study evaluated the clinical utility of recently described NLR, PLR, and MLR on prognosis in children with HL.

The immune system and inflammation in HL have been known for many years and have attracted a lot of attention from many researchers. The hematological

Table 3 - The changes of lymphocyte count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratios according to clinical and laboratory features.

Clinical and laboratory features	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
B symptoms, mean±SD								
Absent (n=30)	2490.8±927.4	0.167	2.11 (0.46-8.9)	0.003*	137.6 (76.7-425.0)	0.017*	0.29 (0.06-0.8)	0.005*
Present (n=22)	2084.9±1158.3		4.67 (0.75-56.5)		218.3 (9.96-2235.0)		0.38 (0.05-2.5)	
Bulky disease								
Absent (n=42)	2320 (400-4920)	0.007*	2.5 (0.46-7.75)	0.002*	139.5 (9.96-812.5)	0.001*	0.3 (0.05-2.5)	0.057
Present (n=10)	1560 (200-5250)		7.46 (1.34-56.5)		343.6 (87.62-2235.0)		0.37 (0.21-1.5)	
Erythrocyte sedimentation rate, mean±SD								
≤40 mm/h (n=27)	2429.0±1061.6	0.434	2.12 (0.46-56.5)	0.042*	140.9 (9.96-2235)	0.268*	0.29 (0.05-1.5)	0.043*
>40 mm/h (n=25)	2200.4±1025.2		3.42 (0.75-8.0)		165.87 (77.39-812.5)		0.35 (0.12-2.5)	
Lactate dehydrogenase								
≤2 x UNL (n=48)	2250 (200-5250)	0.655*	2.76 (0.46-56.5)	0.31*	152.3 (9.96-2235.0)	0.180*	0.3 (0.05-1.5)	0.216
>2 x UNL (n=4)	2250 (400-2780)		5.45 (1.15-8)		274.26 (130.74-812.5)		0.56 (0.23-2.5)	
Stage								
II (n=22)	2260 (1160-5250)		2.62 (0.46-13.1)		139.5 (9.96-343.6)		0.29 (0.13-0.67)	
III (n=24)	2200 (200-4080)	0.323*	2.7 (0.57-56.5)	0.166*	171.9 (76.7-2235.0)	0.079*	0.3 (0.05-1.5)	0.064*
IV (n=6)	1800 (400-2900)		5.41 (2.1-8)		256.0 (109.3-812.5)		0.38 (0.27-2.5)	
Risk group								
Low (n=15)	2225 (1160-5250)		1.85 (0.46-4.33)		138.03 (87.62-258.62)		0.25 (0.13-0.45)	
Intermediate (n=16)	2350 (1000-4080)	0.415*	2.88 (0.57-13.09)	0.117*	173.53 (76.67-425.0)	0.103*	0.3 (0.06-0.8)	0.043*
High (n=21)	2105 (200-4920)		3.42 (0.75-56.5)		171.86 (9.96-2235.0)		0.36 (0.05-2.5)	
Outcomes								
Alive (n=48)	2300 (1000-5250)	0.004*	2.65 (0.46-13.09)	0.017*	146.5 (9.96-523.1)	0.004*	0.3 (0.05-0.83)	0.008*
Dead (n=4)	780 (200-1850)		6.82 (3.28-56.5)		543.0 (258.6-2235)		0.98 (0.37-2.5)	

*Since the distribution of these variables was not normal, non-parametric tests were used. Also, median plus minimum-maximum values were given as descriptive statistics for these variables. UNL: upper normal limit, SD: standard deviation

Table 4 - Evaluation of the factors effect on survival analyzes.

Variables	Overall survival		
	Estimate	SE	*P*-values
B symptoms			
Absent (n=30)	96.0	3.5	0.229
Present (n=22)	85.2	8	
Bulky disease			
Absent (n=42)	94.9	3.5	0.088
Present (n=10)	71.1	18	
Erythrocyte sedimentation rate			
≤40 mm/h (n=27)	91.5	5.8	0.996
>40 mm/h (n=25)	90.4	6.6	
Hemoglobin			
Normal (n=33)	92.2	5.2	0.632
Anemia (n=19)	89.2	7.2	
Leukocyte counts			
Normal (n=37)	91.2	4.8	0.852
High (n=11)	87.5	11.7	
Low (n=4)[a]			
Neutrophil counts			
Normal (n=31)	93.1	4.7	0.857
High (n=21)	87.2	8.6	
Lymphocyte counts			
Normal (n=44)	96.7	3.7	<0.0001
Low (n=8)	60.0	18.2	
Monocyte counts			
Normal (n=32)	89.0	6.1	0.842
High (n=17)	93.3	6.4	
Low (n=3)[a]			
Platelet counts			
Normal (n=40)	91.9	4.5	0.96
High (n=11)	87.5	11.7	
Low (n=1)[a]			
Neutrophil-to-lymphocyte ratio			
≤3.17 (n=29)	100	-	0.018
>3.17 (n=23)	78.6	9.7	
Platelet-to-lymphocyte ratio			
≤180 (n=30)	100	-	0.009
>180 (n=22)	76.5	10.6	
Monocyte-to-lymphocyte ratio			
≤0.29 (n=23)	100	-	0.059
>0.29 (n=29)	83.1	7.9	
Risk group			
Low (n=15)	92.9	6.9	0.895
Intermediate (n=16)	90.9	8.7	
High (n=21)	90.2	6.6	

[a]Since the number of patients in this group was small, they were not included in this analysis.
SE: standard error

abnormalities in HL are anemia, thrombocytopenia, neutrophilia or neutropenia, eosinophilia, and lymphopenia.[2]

Lymphopenia in HL has been known for a long time. The frequency of lymphopenia in HL is highly variable and has been known to be between 6.4-20.7%.[20-24] Although the above-mentioned prognostic factors are not so emphasized in HL, studies have shown the prognostic significance of lymphopenia, but the experience in children was unfortunately not as much as in adults. In all these studies, lymphopenia was seen as an unfavorable prognostic factor.[20-24] In our study, the

frequency of lymphopenia, defined as being below the lower limit for that age group, was 15.1%. Furthermore, when the effect of lymphopenia on overall survival rates was investigated, the overall survival rates of children with normal lymphocyte counts was 96.8% and 60.0% with lymphopenia, and the difference was statistically significant. Although it was not seen as a risk factor in the multivariate analysis in our study, lymphopenia was discovered to be a risk factor in the multivariate analysis in a study by Bhethanabhotla et al.[23]

Recently, NLR is a marker employed in different disease groups, especially some rheumatologic and malignant diseases. These are studies that sometimes help in disease diagnosis and indicate their relationship with the severity of the disease.[8-16] There is more experience on this subject in adulthood. While the NLR and PLR values of both pediatric and adult patients with osteosarcoma were statistically higher than the control group, the lymphocyte-to-monocyte ratio was lower than the control group. In a previous study, they emphasized that the elevation of these biomarkers was a factor that negatively affected the overall survival rate.[11] Another study in patients with osteosarcoma demonstrated the prognostic significance of NLR.[13] In a study carried out in pediatric and adult patients with medulloblastoma, increased preoperative NLR and PLR were unfavorable prognostic factors, and no effect of preoperative MLR on prognosis was detected.[14] Similarly, NLR was significantly associated with prognosis in pediatric patients with parotid cancer.[15] However, in neuroblastoma, the authors determined no predictive value of NLR, PLR, and MLR on the overall survival rate.[12] In our study, NLR, PLR, and MLR values of patients with B symptoms were higher than those without B symptoms. While the lymphocyte counts were lower in patients with bulky disease, NLR and PLR values were found to be higher. Another feature was that while the lymphocyte counts were lower in dead patients, NLR, PLR, and MLR values were higher. As the effect on survival analysis was examined, these markers did not affect event-free survival. However, in univariate analysis, we discovered that low lymphocyte counts, and high NLR and PLR values had an unfavorable effect on overall survival rates. Cox regression analysis revealed that tumor lymphocyte counts, NLR, and PLR, which are all prognostic factors in univariate analysis, are not prognostic risk factors. The lymphocyte count plays a critical role in the changes in NLR, PLR, and MLR. Vasquez et al[17] emphasized that in pediatric patients with sarcoma, absolute lymphocyte count recovery and NLR were independent prognostic factors.

Study limitation. The significant limitation in this study is the small number of dead patients and the low number of patients, especially in the subgroups.

In conclusion, the change in lymphocyte count, NLR, PLR, and MLR may be related to the reflection of the immune system and inflammation, which contributes to cancer development and behavior. These markers can help predict prognosis in children with HL. However, larger pediatric studies are needed.

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