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Research Article

Prognostic Significance of *Combined Inflammatory Index (CII)* in Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Abstract

Objectives: Inflammatory indexes are shown to have clinical significance in cancer. We aimed to determine the prognostic significance of a novel scale index as *combined inflammatory index (CII)* including leukocyte/lymphocyte ratio(LLR) & prognostic nutritional index(PNI) in nodular lymphocyte predominant Hodgkin Lymphoma(NLPHL) comparing them with well-known prognostic factors.

Methods: 101 patients were evaluated retrospectively. Cut-offs were 3.9 for LLR and 53.5 for PNI by ROC analyses. A novel scale-index ('combined inflammatory index-CII') was obtained by the combination of LLR and PNI.

Results: There was a moderate negative correlation between PNI and LLR (r=-0,66). In univariate analyses, advanced stage, bone marrow infiltration(BMI), B symptoms, lymphocytopenia, hypoalbuminemia, higher LLR(≥3.9) and lower PNI(≤53.5) were found to be significant prognostic factors. In multivariate analyses, LLR, PNI and CII were found to be independent significant risk factors for PFS while the models were standardized by age, stage, anemia, hypoalbuminemia, B symptoms & bulky disease.

Conclusion: Prognostic score examining LLR and PNI besides other clinical parameters showed that patients in high risk group (higher LLR and lower PNI) had shortest PFS. In conclusion, a scoring system combining LLR and PNI is a novel scoring system in NLPHL.Combined inflammatory index-CII can be used as a prognostic factor in NLPHL.

Keywords: Combined inflammatory index, CII, LLR, nodular lymphocyte predominant hodgkin lymphoma, PNI

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Nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) accounts 5% of the cases with Hodgkin Lymphoma (HL) and the majority of the cases are presented with early stage disease, but late relapses and transformation to diffuse large B-cell lymphoma are not uncommon. Therapeutic approach differs from classic HL (cHL) by CD20 expression without CD30 expression frequently presenting with limited stage disease and optimal therapy is not clear in NLPHL.[1]

More powerful prognostic indicators and/or scores are needed to find out the most appropriate treatment modality and to predict the clinical outcome in this unique entity.

Neutrophil lymphocyte ratio (NLR) is a poor prognostic indicator in cHL.[2-5] The prognostic significance of different inflammation parameters including lymphocyte/platelet ratio (LPR), platelet/lymphocyte ratio (PLR), neutrophil/platelet ratio (NPR), prognostic nutritional mindex (PNI) were reported in some hemopoietic neoplasias previously.[6-15] However, the prognostic role of these inflammatory indexes was not well documented in NLPHL, an enitity that differs from cHL. Therefore, we aimed to explore the prognostic significance of inflammatory indexes such as leukocyte/lymphocyte ratio (LLR) & prognostic nutritional index (PNI) and define novel prognostic factors for NLPHL besides evaluation of well-known prognostic indicators in cHL.

Methods

A retrospective multicenter study was conducted in Turkey. A total of 111 patients from 10 centers were evaluated retrospectively. A total of 101 cases diagnosed with NLPHL by experienced hematopathologists were included in the study. Clinicopathological characteristics (i.e. age, sex, stage, bone marrow infiltration (BMI), B symptoms, bulky disease and response to therapy) and laboratory values (i.e. albumin, hemoglobin, lymphocyte, leukocyte) of the patients were recorded from patients' follow-up files data.

Hypoalbuminemia, anemia, leucocytosis and lymphopenia are poor prognostic factors for cHL. Albumin <4g/dl was determined as hypoalbuminemia, and hemoglobin <10.5g/dl was determined as anemia as reported for cHL. Two different cut-off points were used for leukocytosis (WBC >10.10^9/L and >15.10^9/L), and lymphocytopenia (lymphocyte count <1x10^9/L and <0,6x 10^9/L).

LLR and PNI were calculated to evaluate as prognostic indicators rather than known prognostic indicators. LLR was calculated by dividing the peripheral blood levels of absolute leukocyte count by absolute lymphocyte count at diagnosis. PNI was calculated as 10×serum albumin (g/dl) + 0.005 × total lymphocyte count/mm^3 at diagnosis.

Possible alternative cut-off points for the LLR and PNI were evaluated by using AUC (area under ROC curve) statistics and median values of the variables distributions. Cut-off points based on ROC analysis were defined as 3.9 for LLR and 53.5 for PNI. They were defined as 3.6 for LLR and 55.1 for PNI according to median values of the variables distribution, respectively. Cut-off points detected by ROC analysis and median values were found to be close to each other, thus the cut off values detected by ROC analyses were used for statistical analyses (3.9 for LLR & 53.5 for PMI). LLR was lower than 3.9 in 61 cases whereas PNI was higher than 53.5 in 63 cases. ROC analysis for LLR and PNI was shown in figure 1.

Risk classification was performed based on LLR & PNI combination. Four risk groups were defined as low risk group (low LLR <3.9 & high PNI >53.5, risk negative for both LLR and PNI); intermediate risk group (low LLR<3.9 & low PNI ≤53.5, risk positive for LLR and negative for PNI), high-intermediate risk group (LLR≥3.9 & high PNI>53.5, risk negative for for LLR and positive for PNI) and high risk group (LLR≥3.9 & low PNI≤53.5, risk positive for both LLR and PNI) (model 1). There was no significant difference between intermediate and high-intermediate risk groups in both univariate and multivariate analyses, therefore these two risk groups (i.e. intermediate and high-intermediate risk groups) were gathered , so risk reclassification was de-

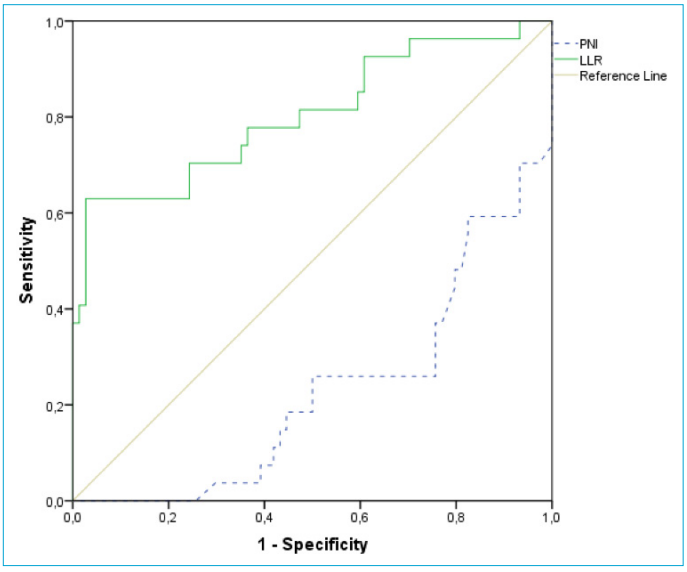

Figure 1. ROC analysis for Prognostic Nutritional Index and Leukocyte Lymphocyte Ratio.

Cut-off or Prognostic Nutritional Index (PNI): 53,5 (sensitivity 74%, specificity 75 %, AUC: 0,77), Cut-off or Leukocyte Lymphocyte Ratio (LLR):3,9 (sensitivity 70% specificity 76%, AUC:0,80).

fined as 3 groups (low, intermediate and high risk groups, model 2). A new prognostic scale-score was obtained from combination of LLR and PNI, this prognostic score was named as '*combined inflammatory index (CII)*'. It was constructed by utilizing these significant factors in univariate and multivariate analyses to classify the patients into 3 risk groups; low (score=0), intermediate (score=1), and high (score=2) risk groups based on number of risk factors.

Treatment modalities and regimens were also recorded since these patients had been treated in different centers. Treatment modalities were as observation, chemotherapy, rituximab & radiation according to the stage.

Statistical Analysis

The correlation between continuous variables was analyzed by Spearman correlation test. Chi square test or Student t test were used to compare the groups. Possible alternative cut-off points for the LLR and PNIwere evaluated using AUC (area under ROC curve) statistics and median values of the distributions of the variables. The prognostic ability of individual LLR and PNI factors wereevaluated for PFS in both univariate and multivariable Cox regression models. PFS was defined as the time from diagnosis to the time of any documented clinical progression, relapse, or death from any cause. The Kaplan-Meier method and Cox proportional regression model were used to estimate the mean-median survival rates, failure rates, hazard ratios (HRs). Log-rank test was used to compare the survival distributions between groups. The results were reported as mean±SD, median, number (n) and percent (%). A p value <0.05 was considered as significant. The analyses were performed using the statistical package SPSS v 22.0.

Results

Female-to-male ratio was 0.71 (n=42/59). Mean age was 39.9±12.5 (16-73) years with a median follow up as 27 months (1-163 months). Two thirds of the patients were younger than 45 years. Ninety percent of the cases presented with lymph node involvement while 10 patients had extranodal involvement. Interestingly 8 patients had parotid involvement. Seventy three cases had early stage disease while 8 cases had bone marrow involvement, 22 had B symptoms and 11 had bulky disease. Leukocytosis was detected in 15 cases and 4 cases had both higher leucocyte count according to both upper limits (i.e. leucocyte >10x10^9/L and >15 x10^9/L), respectively. Lymphocytopenia was detected in 8 patients and 3 cases had lymphocytopenia according to both lower limits (i.e. lymophocyte <1x10^9/L, and <0,6x 10^9/L), respectively.

Mean value was 54.5±6.4 and median was 55.1 (29.1-68.0) for PNI whereas mean level of LLR was 4.1±2.4 and median value was 3.6 (1.1-15.3). There was a moderate negative correlation between PNI and LLR (r=-0.66).

Table 1 shows demographic and clinical features of the patients. In univariate analyses; B symptoms (p=0.005), BMI (p=0.017), lymphocytopenia (p=0.006), hypoalbuminemia (p=0.038), response to therapy (p=0.001), LLR <3.9 (p=0.0001) and PNI >53.5 (p=0.0001) were found to be significant. Albumin (p=0.045), lymphocyte (p=0.0001), PNI (p=0.0001) and LLR (p=0.0001) were also found to have be significantly difference between good (alive without event) and poor (with event: ex/relapse/remission) prognostic groups. Neither mean level of leukocyte nor ratio of leukocytosis were found to affect the prognosis(p=0.369, p=0.531, respectively).

Seventy four cases were progression free at the time of survival analysis. Relapse had been detected in 27 cases and death occurred in 2 cases. Overall survival analysis could not have been performed due to low number of deaths. Eighty five cases had chemotherapy, such as ABVD (n=77), R-CHOP (n=6), R-ABVD (n=1) and CHOP (n=1). One case had been treated by rituximab alone. Radiation had been given to 40 cases and 3 cases had been followed up with observation only.

Progression free survival was found to be significantly longer in cases with early stage disease (p=0.010), without BMI (p=0.0001), with response to therapy (p=0.0001), with low LLR (<3.9) (p=0.015) & high PNI (>53.5) (p=0.0001). It was shorter in cases with advanced stage disease (p=0.002), BMI (p=0.001), leukocytosis with >15x109/L upper limit but not with >10x10^9/L limit (p=0.028 and p=0.322; respectively), lymphocytopenia with both lower limits as <1x10^9/L and <0.6x10^9/L (p=0.006 and p=0.001; respectively), anemia (p=0.001), hypoalbuminemia (p=0.040), high LLR (≥3.9) (p=0.0001) and low PNI (≤53.5) (p=0.0001). Progression free survival according to LLR & PNI is shown in figure 2 (2A, 2B). Progression free survival is also evaluated according to the PNI and LLR 'combined' risk classification groups (Fig. 3). The patients with low LLR & high PNI were found to have longest PFS while the others with high LLR & low PNI had shortest PFS. Mean values for PFS were as 124 months & 119 months for the patients with low LLR & high PNI while median values were as 31.6 months & 10.1 months for those with high LLR & low PNI, respectively. We consider that PFS advantage of the patients with low LLR & high PNI is the remarkable point of our study. Scale covering LLR and PNI was named as 'combined inflammation index (CII)'. Mean and median PFS according to these factors are shown in Table 2.

Table 1. Demographic and clinical features of the patients according to prognosis

	Prognosis				
	Poor (exitus or remission or relapse)		Good (Alive without event)		
	n	%	n	%	p
Sex					
Female	8	(29,6)	34	(45,9)	
Male	19	(70,4)	40	(54,1)	0,141
Stage					
I	3	(11,1)	17	(23,0)	
II	13	(48,1)	40	(54,1)	
III	5	(18,5)	10	(13,5)	
IV	6	(22,2)	7	(9,5)	0,224
Stage					
Early (I+II)	16	(59,3)	57	(77,0)	
Advanced (III+IV)	11	(40,7)	17	(23,0)	0,077
Bone Marrow Involvement (BMI)					
No	22	(81,5)	71	(95,9)	
Yes	5	(18,5)	3	(4,1)	0,017
B Symptom					
No	16	(59,3)	63	(85,1)	
Yes	11	(40,7)	11	(14,9)	0,005
Bulky disease					
No	23	(85,2)	67	(90,5)	
Yes	4	(14,8)	7	(9,5)	0,445
Leukocytosis (>10x10^9/L)					
No	22	(81,5)	64	(86,5)	
Yes	5	(18,5)	10	(13,5)	0,531
Leukocytosis (>15x10^9/L)					
No	25	(92,6)	72	(97,3)	
Yes	2	(7,4)	2	(2,7)	0,283
Lymphocytopenia (<1x10^9/L)					
No	21	(77,8)	70	(94,6)	
Yes	6	(22,2)	4	(5,4)	0,012
Lymphocytopenia (<0.6x10^9/L)					
No	24	(88,9)	74	(100,0)	
Yes	3	(11,1)	0	(,0)	0,004
Anemia (<10,5)					
No	23	(85,2)	71	(95,9)	
Yes	4	(14,8)	3	(4,1)	0,060
Albumin (<4,0)					
No	19	(70,4)	65	(87,8)	
Yes	8	(29,6)	9	(12,2)	0,038
Leukocyte Lymphocyte Ratio (LLR)					
Low (<3,89)	8	(29,6)	53	(71,6)	
High (≥3,9)	19	(70,4)	21	(28,4)	0,0001
Prognostic Nutritional Index (PNI)					
Low (>53,5)	7	(25,9)	56	(75,7)	
High (≤53,5)	20	(74,1)	18	(24,3)	0,0001

Table 1. CONT.

	Prognosis				
	Poor (exitus or remission or relapse)		Good (Alive without event)		
	n	%	n	%	p
Response to therapy					
Complete	16	(59,3)	60	(81,1)	
Partial	5	(18,5)	7	(9,5)	
No response	5	(18,5)	0	(,0)	
Unknown	1	(3,7)	7	(9,5)	0,001
	Mean	**SD**	**Mean**	**SD**	**p**
Age	37,3	10,9	41,0	13,0	0,193
Hemoglobin	13,9	2,1	14,4	1,4	0,161
Albumin	4,2	0,5	4,4	0,4	0,045
Lymphocyte	1577,0	613,9	2392,6	790,6	0,0001
Leukocyte	8070,0	3157,1	7553,6	2287,0	0,369
Prognostic Nutritional Index-PNI	49,6	7,2	56,3	5,1	0,0001
Leukocyte/ Lymphocyte Ratio-LLR	6,1	3,7	3,4	0,9	0,0001

Two Cox regression models were used for significant parameters in univariate survival analysis. These factors are age, PNI, LLR, stage, bone marrow involvement (BMI), anemia and B symptoms. In model 1, among these parameters only LLR (p=0.023) and PNI (p=0.015) were found to be significant when age, stage, anemia, hypoalbuminemia, BMI, LLR and PNI were evaluated as categorical variables for PFS. In model 2, risk classification of the LLR and PNI combination-scale were included in the equation instead of LNR and PNI. The scale remained significant as a prognostic factor for PFS. p value was found to be >0.05 for intermediate and high-intermedieate (score 1 and 2) groups, however the confidence interval (CI) range was found to be wide for high risk group (score 3). It is significantly correlated with poor prognosis (OR:11.7, 95%CI: 3.0-45.6). Table 3 shows the results of Cox Regression Analyses. According

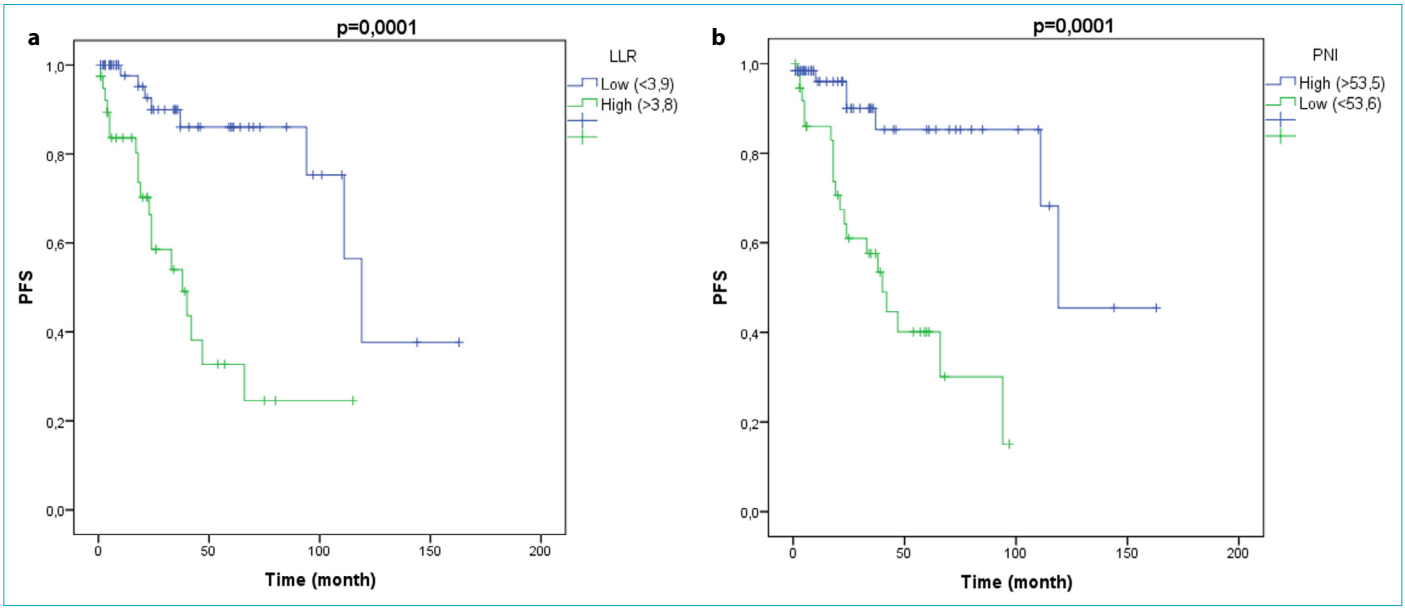

Figure 2. (a) Survival times according to Leukocyte Lymphocyte Ratio. **(b)** Survival times according to Prognostic Nutritional Index.

Leukocyte Lymphocyte Ratio: LLR; PrognosticNutritionalIndex: PNI.

Table 2. Correlations between LLR and PNI with other variables

	LLR	Hemoglobin	Albumin	Lymphocyte	Leukocyte
PNI	-,66**	,33**	,77**	,71**	,06
LLR	1	-,20*	-,42**	-,58**	,31**
Hemoglobin		1	,37**	,10	-,20*
Albumin			1	,10	-,26*
Lymphocyte				1	,37**

PNI: Prognostic Nutritional Index; LLR: Leukocyte Lymphocyte Ratio; (*p<0.01, ** p<0.001.

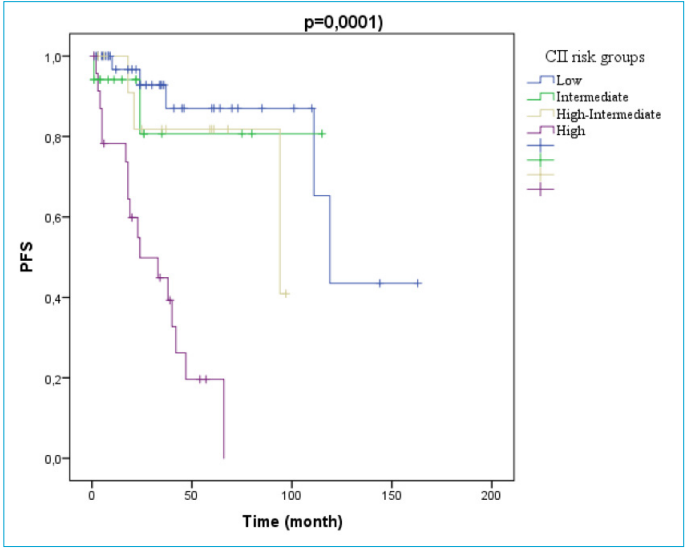

Figure 3. Survival according to Combined Inflammatory Index risk groups (obtained by combined Leukocyte Lymphocyte Ratio and Prognostic Nutritional Index).

Combined Inflammatory Index: CII , Leukocyte Lymphocyte Ratio: LLR , Prognostic Nutritional Index: PNI.

to Cox regression models, the groups of LLR & PNI and also the scale that is obtained from combination of LLR and PNI were found to be independent significant risk factors for PFS while the models were standardized by age, stage, anemia, hypoalbuminemia and BMI.

Table 4 shows the results of the Cox Regression Analyses. Two Cox regression models were obtained with significant parameters detected by univariate survival analysis: (age, stage, Bulky disease, B symptoms, anemia & Hgb level, PNI, LLR were evaluated as categorical variables for PFS). In model 1 among these parameters both LLR (OR:3.6 (95% CI:1.2-10.4, p=0.020) and PNI OR:3.9 (95%CI:1.2-12.8, p=0.023) were found to be significant independent risk factors. In model 2, risk classification of the LLR and PNI combination scale were included in the equation instead of LNR and PNI. The scale remained significant prognostic factor for PFS. While the the p value was found to be >0.05 for intermediate and high intermedieate (score 1 and 2) groups, but the CI range of high risk group (score 3) was found to be wide (OR:12.4 (95%CI:3.0-52.1, p=0.001). According to Cox regression models, the groups of LLR and PNI and also the scale that obtained combination of LLR and PNI were found to be independent significant risk factors for PFS while the models were standardized by age, stage, anemia, hypoalbuminemia, Bulky disease, B symptoms parameters.

Discussion

Nodular lymphocyte predominant Hodgkin Lymphoma is a unique entity with good prognosis with earlier stage presentation. Among our 101 cases, 73 had early stage disease at diagnosis. There is male predominance in NLPHL and median age is around 37 years as if in our study. Majority of the cases are presented with early stage disease and the rate of BM involvement is not so clear due to lack of routine BM biopsy as a staging procedure in all cases in the majority of the series. Agbay et al. reported BMI rate as 9,2% among 262 cases.[16] In that study, BMI was found to be associated with variant histologic type. In the literature, BMI has been found to be associated with shorter event free survival, higher rate of disease recurrence/progression and aggressive clinical outcome.[16-18] In our study, median age was 37 years and only 8 patients had BMI. The patients with BMI has shorter PFS. As expected, PFS was found to be longer for the cases who responded to treatment and for those with early stage at diagnosis, without BMI or lymphocytopenia.

Optimal therapy is not well-known for this unique subtype (i.e. NLPHL) in the literature, so treatment approach is highly variable in our study group. Radiation is a reasonable choice in cases with early stage disease. Chemotherapy is a backbone in the treatment of lymphoma. Fanale et al reported that all of the patients diagnosed with NLPHL had objective response with a complete response (CR) rate of 89% when they were treated with R-CHOP regimen.[19] They added that none of the patients had transformation to an aggressive form of lymphoma. In the literature, CHOP or ABVD regimens with or without rituximab have been

Table 3. Mean and Median PFS according to related factors

	n of Total/ Event	Time Mean/median	p
Sex			
Female	42/8	115,9/ -	
Male	59/19	79,5/94	0,256
Stage			
Early (I+II)	73/16	101,8/111,0	
Adavanced (III+IV)	28/11	39,5/33,0	0,002
Bone marrow involvement (BMI)			
No	93/22	98,0/111	
Yes	8/5	24,4/33	0,001
B Symptom			
No	79/16	102,0/111	
Yes	22/11	49,3/23	0,0001
Bulky disease			
No	90/23	93,6/111	
Yes	11/4	61,1/24,0	0,312
Leukocytosis (>10x10^9/L)			
No	86/22	93,0/111	
Yes	15/5	69,6/-	0,322
Leukocytosis (>15x10^9/L))			
No	97/25	94,0/111	
Yes	4/2	19,3/19	0,028
Lymphocytopenia (<1x10^9/L)			
No	91/21	97.1/111	
Yes	10/6	33,4/24	0,006
Lymphocytopenia (<0.6 x10^9/L)			
No	98/24	95,6/111	
Yes	3/3	19,6/24	0,001
Anemia (<10,5)			
No	94/23	96,6/111	
Yes	7/4	19,5/23	0,001
Alb (<4,0)			
No	84/19	101,0/119,0	
Yes	17/8	51,8/66,0	0,040
Leukocyte Lymphocyte Ratio			
Risk (-) (Lower <3,9)	61/8	118,9/119	
Risk (+) (Higher≥3,9)	40/19	49,7/38	0,0001
Prognostic Nutritional Index			
Risk (-) (Higher>53,5)	63/7	88,9/119	
Risk (+) (Lower ≤53,5)	38/20	47,4/40	0,0001
Risk Groups Model 1			
CII (Combined LLR and PNI)			
0 Low (risk - for both LLR and PNI)	46/5	124,3/119	
1 Intermediate (risk + for LLR and - for PNI)	17/2	96.0/-	
2 High-Intermediate (risk - for LLR and + for PNI)	14/3	81,6/94	
3 High (risk + for both LLR and PNI)	24/17	31,6/10,1	0,001
Risk Groups Model 2			
CII (Combined LLR and PNI)			
0 Low (risk - for both LLR and PNI)	46/5	124,3/119	
1 Intermediate (risk + for LLR or PNI)	31/5	91,4/-	
2 High (risk + for both LLR and PNI)	24/17	31,6/24	0,001

CII: Combined Inflammatory Index.

Table 4. Results of the Cox Regression Analyses

	B	SE	Wald	df	p	OR	95,0% CI for OR	
							Lower	Upper
Model 1								
Age>45	-0,043	0,020	4,485	1	0,034	1,0	0,9	1,0
Stage (advenced)	0,798	0,488	2,672	1	0,102	2,2	0,9	5,8
B Symptom (yes)	0,805	0,507	2,514	1	0,113	2,2	0,8	6,0
Bulky	0,117	0,612	0,036	1	0,849	1,1	0,3	3,7
Hemoglobin <10,5	0,907	0,624	2,109	1	0,146	2,5	0,7	8,4
Alb <4,0	0,134	0,519	0,067	1	0,796	1,1	0,4	3,2
LLR (Higher≥3,9)	1,269	0,547	5,379	1	0,020	3,6	1,2	10,4
PNI (Lower≤53,5)	1,367	0,602	5,162	1	0,023	3,9	1,2	12,8
Model 2								
Age>45	-0,041	0,020	4,057	1	0,044	1,0	0,9	1,0
Stage (advenced)	0,800	0,486	2,711	1	0,100	2,2	0,9	5,8
B Symptom (yes)	0,801	0,519	2,381	1	0,123	2,2	0,8	6,2
Bulky	0,105	0,616	0,029	1	0,865	1,1	0,3	3,7
Hemoglobin <10,5	0,879	0,625	1,978	1	0,160	2,4	0,7	8,2
Alb <4,0	0,092	0,523	0,031	1	0,860	1,1	0,4	3,1
PNI and LLR								
0 Low			13,798	3	0,003			
						Ref.		
1 Intermediate	0,804	0,912	0,776	1	0,378	2,2	0,4	13,4
2 High-Intermediate	1,024	0,832	1,515	1	0,218	2,8	0,5	14,2
3 High	2,519	0,732	11,837	1	0,001	12,4	3,0	52,1

reported as therapeutic options for many patients, however which one is the best for these patients is stil unclear though rituximab is claimed to be one step ahead at least in terms of PFS.[19-21] Majority of the cases have been found to be at early stage and one third of them have been followed up without any treatment or had only local radiotherapy.[22] Radiation therapy is an option in early stage disease. In our study, only three cases had been treated by radiation only while 37 cases had radiation in addition to systemic chemotherapy. Chemotherapy had been given to majority of our cases and most common regimens were ABVD or CHOP. Three cases had been followed up without any local or systemic therapy. This therapeutic strategy in our study group might be related to the lack of a 'standard' treatment modality of NLPHL and treatment approaches had been adapted from cHL treatment by analogy. Response to first line therapy was achieved in 95% of our cases in parallel to the literature. Rituximab is a reasonable choice for these NLPHL cases due to CD20 expression, but it had been used in only 9 cases due to the re-imbursement problem in our country.

Tumor microenvironmet contributes to tumor promotion, proliferation and progression via various growth factors and inflammatory cytokines.[23-25] It has also a critical role in tumor biology of hemaotopoietic malignancies such as HL contributing to tumor progression and migration of tumor cells by activation of signaling pathways.[23-25] On the other hand, lymphocytes were shown to have antitumor effect.[25] In recent years, many inflammatory indexes such as neutrophil lymphocyte ratio (NLR), derived neutrophil lymphocyte ratio (DNLR), platelet lymphocyte ratio (PLR) and prognostic nutritional index (PNI) have been suggested as prognostic markers for various malignancies with different cut off values.[5, 6,10-13,26-29] In a retrospective study covering 312 cases with cHL, high NLR (≥4.3) has been found to be correlated with poor OS and advanced stage.[2] It was defined as an independent prognostic factor in multivariate analysis, so they added that NLR might have been used as a simple and inexpensive index in cHL. Marcheselli et al. reported that nodular sclerosing type cHL patients with higher NLR (NLR >6) had significantly shorter PFS and OS.[4] It was supported by another study including 338 cases with stage I-II cHL.[3] In that study NLR with a cut off value as 6,4 has been determined as a poor prognostic factor for freedom from progression (i.e. patients with NLR (>6.4) had poor outcomes).[3] Neutrophil lymphocyte ratio (NLR) has been found to have prognostic significance for '*cHL*', however data for the prognostic value of NLR in '*NLPHL*' is not so clear.

In present study, we considered that LLR besides NLR

might have prognostic significance in NLPHL. In addition to tumor microenvironmet, profile of peripheral blood cells including eosinophils, monocytes, lymphocyte, macrophage and dendritic cells may have critical role in neoplastic process and clinical outcome of the patients with HL.[2, 6, 30-36] On the other hand, leukocytosis and lymphocytopenia in the peripheral blood have been found to be prognostic indicators for both cHL and NLPHL. Therefore, we considered to evaluate the prognostic value of other inflammatory ratios such as LLR. We compared the correlation and prognostic significance of LLR with other prognostic indicators and inflammation indexes, such as PNI. Cut off point for LLR in our study has been determined as 3.9 and LLR was found to have prognostic value as a prognostic inflammatory index in NLPHL in multivariate analysis. The patients with highr LLR (>3.9) had poor prognosis in paralel to other peripheral blood abnormalities, such as anemia, lymphocytopenia, leukocytosis and hypoalbuminemia in both cHL and NLPHL. We consider that LLR is a cheap and easily calculated prognostic index fort he patients diagnosed with NLPHL. In fact, we tested LLR and NLR in our previous study covering cHL and we found the prognostic significance of LLR in addition to NLR (Unpublished data).

Prognostic nutritional index is a marker of host inflammatory and nutritional status and it has been shown to be a prognostic factor with variable cutoff values for long term outcomes in various solid tumors.[27,37,38] It has been well clarified that albumin helps assesment of disease progression & severity while lymphocytes have critical role in the host immune response to eradicate the occurrence and progression of tumors previously.[39] Lower PNI reflects lower levels of albumin as an underlying mechanism for clinical significance of PNI as a prognostic factor. Cut off value for PNI may differ in various studies according to ROC analysis in each of them, but it is usually set as 45 since PNI (<45) is frequently defined as 'moderate to severe' malnutrition. However, the optimal cut off value for PNI to predict the long-term outcomes as a prognostic factor remains unclear. Low PNI (<52.8) has been reported as an independent poor prognostic factor in breast cancer with shorter OS and higher recurrence rates.[40] In another study covering 215 cases with HIV infected lymphoma, PNI has been found as an independent prognostic factor for OS in correlation with other prognostic factors such as Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS) and Prognostic Index (PI).[14] Lee et al defined cut off value for PNI as 45 in 88 cases with follicular lymphoma.[15] They reported that the patients with high PNI had a higher complete response rate (75.4% vs 43.5%) and better PFS. Higher PNI at relapse was found as a predictor of better post-progression survival.[15] These results suggest that PNI is a significant prognostic inflammatory index for both solid tumors and hemopoietic neoplasias. In our study, ROC analysis defined cut off value for PNI as 53.5 (sensitivity 74%, specificity 75 %, AUC: 0,77). We demonstrated that PNI is a significant prognostic indicator in NLPHL for the first time and we documented a significant association between LLR and PNI.

Prognostic factors in NLPHL are not so clear although they are well defined in cHL. Male sex, splenic involvement, advanced stage, rituximab without chemotherapy, variant histology, bigger tumor size (>5cm) have been found as poor prognostic factors in NLPHL.[19,41-43] A unique prognostic score has been proposed by GHLSG when they analyzed 423 patients with NLPHL.[42] They reported that variant histologic growth pattern, advanced stage (especially stage IV), male gender, splenic involvement, low serum albumin level (<4g/dl) and low hemoglobin level (<10.5g/dl) were found to be associated with increased risk for progression and/or relapse in univariate regression analyses. In final analysis, male gender (score point 2), low serum albumin (score point 1) and variant histologic growth pattern (score point 1) were found to be independent risk factors for progression or relapse . Three risk groups have been proposed according these scores. Score 0-1 was assessed as low risk, score 2 was assessed as intermediate risk and score 3-4 was assessed as high risk groups. There were significant differences in PFS and OS among these 3 risk groups.[42]

In our study group, variant histology could not be determined due to retrospective and multicentric nature of our study. Despite indolent clinical outcome, there is no sufficient data about the biology of NLPHL.We assessed PNI and LLR in addition to the well-known prognostic indicators and we found these 2 inflammation indexes as the most important prognostic indicators. At this point, we evaluated PFS according to PNI & LLR. The patients with low PNI and high LLR had shortest PFS whereas the others with low PNI and high LLR had longest PFS. Then, we obtained a novel scoring system by using these inflammatory indexes (i.e. PNI & LLR) & called it as '*combined inflammatory index (CII)*' as we mentioned before. However, LLR & PNI can not be considered independent from each other since they are both based on lymphocytes counts.

In conclusion, we consider that combining these two inflammatory indexes (i.e. PNI & LLR) and using this novel scoring system (i.e. CII) might contribute to the prediction of prognosis in NLPHL easily. The scale must be confirmed with larger studies enabling detailed statistical analyses. Further clinical trials are needed to increase the strength of the cohort with longer follow-up.

Disclosures

Ethics Committee Approval: This study had ethical approval from Cukurova University Ethical Commitee.

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Authorship Contributions: Design – S.P.; Data collection &/or processing – S.P., M.K.C., I.B., G.S., M.P., M.D., F.A., S.C., A.U., B.Y., S.L., H.O., B.U.U., O.A., S.B., M.O., I.G., N.K.B., Z.B., N.K., M.Y., H.A.; Analysis and/or interpretation – G.S.; Writing – S.P., M.K.C., I.B., G.S., M.P., M.D., F.A., S.C., A.U., B.Y., S.L., H.O., B.U.U., O.A., S.B., M.O., I.G., N.K.B., Z.B., N.K., M.Y., H.A.

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