Original Article

Prognostic Role of Neutrophil to Lymphocyte Ratio at Diagnosis in Patients with Diffuse Large B-Cell Lymphoma

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Received: 08-Oct-2023;
Revision: 31-May-2024;
Accepted: 25-Jul-2024;
Published: 26-Aug-2024

ABSTRACT

Background: Aim to investigate the prognostic value of neutrophil to lymphocyte ratio (NLR) at the time of diagnosis, which is an inexpensive and easily accessible parameter, compared to factors known as prognostic value (such as R-IPI and NCCN-IPI) in patients with diffuse large B-cell lymphoma (DLBCL). **Aim:** Prognostic value of NLR at diagnosis in DLBCL. **Methods:** A hundred (100) newly diagnosed DLBCL patients were included. The correlations between the NLR with clinical characteristics, treatment response, and survival were analyzed. The NLR cut-off value was taken at 3.5 according to the receiver operating characteristic curve. **Results:** There were 53 patients with an NLR of 3.5 and 47 patients with an NLR < 3.5. Patients with NLR ≥ 3.5 had a complete response (CR) rate of 66.0% (n = 31/47), and patients with NLR < 3.5 had a CR rate of 98.1% (n = 51/52). The median progression-free survival (PFS) was 132.5 months (95%CI 103.1–162.0). PFS in the NLR ≥ 3.5 group (36 months) was significantly (P < 0.000) shorter than in the NLR < 3.5 group (185 months). The median overall survival (OS) for NLR ≥ 3.5 and NLR < 3.5 was 79.2 months (95% CI 51.6–106.8) and 197.8 months (95% CI 173.2–222.5), respectively. NLR ≥ 3.5 was associated with worse OS than NLR < 3.5 (P = 0.000). The high value of NLR (≥3.5) had lower treatment response rates, higher relapse, and death rates. **Conclusion:** High NLR was associated with poor treatment response, PFS, and OS. NLR can be used as a cost-effective and easy-to-interpret prognostic marker in DLBCL patients.

Keywords: *DLBCL, NLR, prognosis, overall survival, progression-free survival*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma, in 25% to 30% of whole cases.[1-3] Approximately, 150,000 patients are diagnosed with DLBCL worldwide each year.[4] Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard treatment for DLBCL. With this treatment, two-thirds of patients achieve long-term remission.[5,6] Although R-CHOP chemotherapy had a significant effect on survival and increased cure rates of DLBCL, 30%–50% of DLBCL patients resist or relapse after R-CHOP treatment.[7,8] The international prognostic index (IPI) was developed to determine the prognosis and choose the best treatment strategy for DLBCL. IPI was based on age, tumor stage, serum lactate dehydrogenase (LDH) level, performance status, and the number of extranodal disease sites. Unfortunately, IPI was developed in the pre-rituximab era, so it was not possible to adequately identify the group with a poor prognosis.[9] IPI variants such as revised IPI (R-IPI), elderly IPI (E-IPI), National Comprehensive Cancer Network IPI (NCCN-IPI), and biomarker-adjusted IPI (A-IPI) have been developed after-rituximab era, therefore, demonstrated superior

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_726_23

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How to cite this article: Korkmaz G, Ceran F, Dağdaş S, Güneş AK, Sunu C, Pepeler MS, *et al.* Prognostic role of neutrophil to lymphocyte ratio at diagnosis in patients with diffuse large b-cell lymphoma. Niger J Clin Pract 2024;27:1012-9.

prognostic ability in the rituximab era.[10-13] Gene expression profiling and early interim analysis by positron emission tomography were also investigated as prognostic factors.[14,15] However, most of these are costly, difficult to obtain, and difficult to interpret. For this reason, an inexpensive, widely available, and easily interpretable prognostic marker is needed to determine the prognosis of DLBCL.

Modification of the tumor microenvironment is significantly regulated by inflammatory cells. Cancer-induced inflammation and immune response are considered to be critical for tumor progression.[16] Lymphopenia is seen as an indicator of immune dysfunction, while neutrophilia is seen as an indicator of chronic inflammation.[17,18] Neutrophil to lymphocyte ratio (NLR) is a simple parameter to assess easily the inflammatory status of a subject. In our study, we aimed to investigate the prognostic value of NLR at the time of diagnosis, which is an inexpensive and easily accessible parameter compared to other prognostic factors.

Material and Method

Patient and data collection

In our study, we analyzed the NLRs at the time of diagnosis of one hundred DLBCL cases, diagnosed and followed up between 2004 and 2019. Patients younger than 75 years of age received standard doses of R-CHOP, and patients >75 years of age received low-intensity therapies. The study did not include patients with systemic inflammatory disease, active infection, or pregnancy at the time of diagnosis that could affect NLR.

Clinical data

The medical records were reviewed to determine age, gender, LDH level, Eastern Cooperative Oncology Group performance score (ECOG-PS), Ann Arbor stage at diagnosis, R-IPI score, NCCN-IPI score, B symptoms (absent or present), bone marrow involvement, extranodal involvement, and bulky mass. After six cycles of chemotherapy, the treatment responses of the patients were checked by PET/CT, and the responses were recorded according to the Lugano revised response criteria. NLR values were calculated by dividing the neutrophil count by the lymphocyte count in the patient's pre-treatment hemogram. The time from diagnosis to relapse was defined as progression-free survival (PFS). The day of death from any cause or the last day the patient was known to be alive was defined as overall survival (OS).

The study was approved by the Local Ethic Committee. (Ankara Bilkent City Hospital, E1-21-1534,17.Feb. 2021).

Statistical analysis

The distribution of variables was measured by the Kolmogorov-Simirnov test. For the analysis of quantitative independent data, independent samples *t*-test, and Mann-Whitney U-test were used. For the analysis of qualitative independent data, the Chi-squared test was used. To determine the optimal cut-off value for NLR, receiver operating characteristic (ROC) curve analysis was used. Univariate and multivariate logistic regression were used to analyze the level of effect. Cox regression (univariate- multivariate) and Kaplan-Meier were used for the survival analysis. A p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS 28.0.

Results

Baseline clinical characteristics

We evaluated 100 newly diagnosed DLBCL patients, 38 women, and 62 men, with a median age at diagnosis of 52 years. The mean diagnostic NLR was 3.2 (1.2–45.3). Among the patients, 83% responded completely to first-line treatment, and 54% relapsed during follow-up. At a median follow-up of 66 months (5–231), 66% of the patients were alive and 34% of the patients died. Patient characteristics are shown in detail in Table 1.

Cut-off value in the NLR group

Using ROC curve analysis, we determined that a cut-off value of 3.5 was the optimal cut-off point for the NLR [Figure 1].

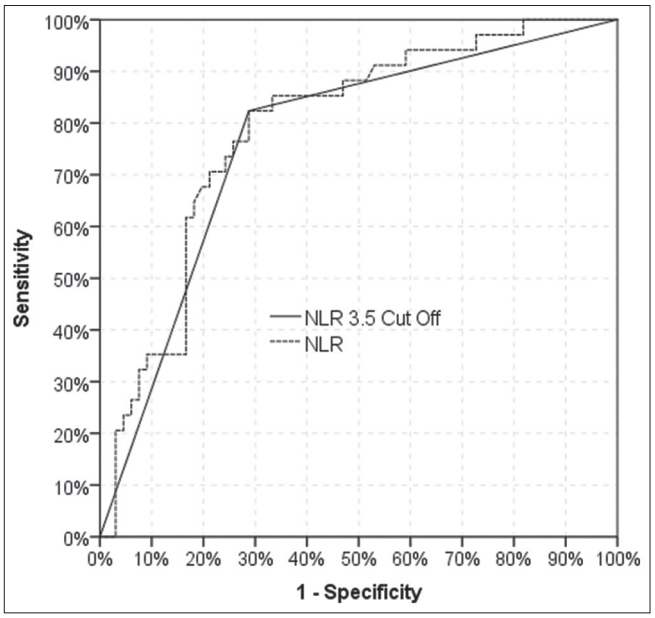

Figure 1: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for NLR (neutrophil to lymphocyte ratio) at diagnosis (AUC = 0.789, $P = 0.000$; 82.4% sensitivity and 71.2% specificity)

Table 1: Patients' characteristics and treatment response

	Min-Max			Median	Mean±sd/n-%		
Age	18.0	-	87.0	52.0	51.0	±	15.9
Sex							
Female					38		38.0%
Male					62		62.0%
NLR	1.2	-	45.3	3.2	4.5	±	5.1
NLR							
< 3.5					53		53.0%
≥ 3.5					47		47.0%
LDH							
Normal					27		27.0%
Elevated, Up To 3x ULN					57		57.0%
> 3x ULN					16		16.0%
ECOG-PS							
< 2					84		84.0%
≥ 2					16		16.0%
Ann Arbor Stage							
I/II					25		25.0%
III/IV					75		75.0%
Extranodal involvement							
None					39		39.0%
1					37		37.0%
> 1					24		24.0%
Bulky Disease							
(-)					79		79.0%
(+)					21		21.0%
R-IPI							
Very Good					23		23.0%
Good					46		46.0%
Poor					30		30.0%
NCCN-IPI							
Low					13		13.0%
Low-Intermediate					47		47.0%
High-ıntermediate					30		30.0%
High					10		10.0%
B symptoms							
(-)					33		33.0%
(+)					67		67.0%
Bone marrow involvment							
(-)					79		79.0%
(+)					21		21.0%
Response							
CR					83		83.0%
PR					5		5.0%
SD					1		1.0%
PD					11		11.0%
Relapse							
(-)					46		46.0%
(+)					54		54.0%
Exitus							
(-)					66		66.0%
(+)					34		34.0%
Follow-up Time	5.0	-	231.0	6.0	70.0	±	49.7

NLR: neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; ULN: Upper Limit of Normal; ECOG-PS: Eastern Cooperative Oncology Group performance score; R-IPI: Revised-International Prognostic Index; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index; CR: Complete Remission; PR: Partial Remission; SD: Stable Diseasae; PD: Progressive Disease

Table 2: Associations between pretreatment NLR and patients characteristics

	NLR <3.5				NLR ≥3.5				p	
	Mean±sd/n-%			Median	Mean±sd/n-%			Median		
Age	48.2	±	15.0	51.0	54.1	±	16.4	54.0	0.061	t
Sex										
Female	20		37.7%		18		38.3%		0.954	X^2
Male	33		62.3%		29		61.7%			
NLR	2.3	±	0.6	2.3	7.1	±	6.5	5.4		
LDH										
Normal	23		43.4%		4		8.5%		0.000	X^2
Elevated, Up To 3xULN	26		49.1%		31		66.0%			
> 3x ULN	4		7.5%		12		25.5%			
ECOG-PS										
<2	50		94.3%		34		72.3%		0.003	X^2
≥ 2	3		5.7%		13		27.7%			
Ann Arbor Stage										
I/II	20		37.7%		5		10.6%		0.002	X^2
III/IV	33		62.3%		42		89.4%			
Extranodal involvement										
None	22		41.5%		17		36.2%		0.857	X^2
1	19		35.8%		18		38.3%			
> 1	12		22.6%		12		25.5%			
Bulky Disease										
(-)	45		84.9%		34		72.3%		0.124	X^2
(+)	8		15.1%		13		27.7%			
R-IPI										
Very Good	22		37.3%		1		2.4%		0.003	X^2
Good	30		50.8%		16		39%			
Poor	7		11.9%		24		58.6%			
NCCN-IPI										
Low	12		22.6%		1		2.1%		0.000	X^2
LI	30		56.6%		17		36.2%			
HI	11		20.8%		19		40.4%			
High	0		0.0%		10		21.3%			
B Semptoms										
(-)	21		39.6%		12		25.5%		0.135	X^2
(+)	32		60.4%		35		74.5%			
Bone marrow involvement										
(-)	42		79.2%		37		78.7%		0.949	X^2
(+)	11		20.8%		10		21.3%			
Response										
CR	52		98.1%		31		66.0%		0.000	X^2
PR	1		1.9%		4		8.5%			
SD	0		0.0%		1		2.1%			
PD	0		0.0%		11		23.4%			
Relapse										
(-)	34		64.2%		12		25.5%		0.000	X^2
(+)	19		35.8%		35		74.5%			
Exitus										
(-)	47		88.7%		19		40.4%		0.000	X^2
(+)	6		11.3%		28		59.6%			
Follow-up Time	93.5	±	47.9	80.0	43.6	±	37.2	31.0	0.000	m

[t]Independent samples t test/[m] Mann-whitney u test/X^2 Chi-square test NLR: neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; ULN: Upper Limit of Normal; ECOG-PS: Eastern Cooperative Oncology Group performance score; R-IPI: Revised-International Prognostic Index; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index; LI: Low-Intermediate; HI: High-Intermediate; CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease

Associations of NLR with clinical characteristics, treatment response, and survival

There were 53 patients with an NLR of 3.5 and 47 patients with an NLR < 3.5. Patients with higher NLR (≥3.5) showed higher disease stage (P = 0.002), lower ECOG-PS (P = 0.003), and higher LDH levels at diagnosis (P = 0.000). Patients with high NLR (≥3.5) were significantly correlated with high R-IPI and NCCN-IPI scores (P = 0.003, P = 0.000, respectively). As shown in Table 2, there was no significant difference between the two groups in terms of age, gender, extranodal involvement, bulky disease, bone marrow involvement, and presence of B symptoms (P > 0.05). Complete response (CR) was achieved in 83 patients, partial response in 5, stable disease in 1, and 11 patients had progressive disease. Patients with NLR ≥ 3.5 had CR rates of 66.0% (n = 31/47), and patients with NLR < 3.5 had CR rates of 98.1% (n = 51/52). The group with high NLR showed lower response rates (CR rate 98.1% in patients with low NLR, 66% in patients with high NLR, P = 0.000) and higher relapse (35.8% in patients with low NLR, 74.5% in patients with high NLR, P = 0.000) and mortality (11.3% in patients with low NLR, 59.6% in patients with high NLR, P = 0.000) rates compared to the other groups [Table 2].

On univariate analysis, NLR (P = 0.000), NCCN-IPI scores (P = 0.010), Ann Arbor Stage (P = 0.028), LDH level (P = 0.012), end of treatment response (P = 0.000) were significantly associated with PFS. However, only the pre-treatment NLR 3.5 cut-off (P = 0.000) was significantly as an independent prognostic factor according to multivariate analysis [Table 3].

The median PFS was 132.5 months (95% CI 103.1-162.0). PFS in the group with NLR ≥ 3.5 (36 months) was

Table 3: Univariate and Multivariate Cox regression analysis for PFS

Factor	Univariate analysis					Multivariate analysis				
	HR	95% CI			p	HR	95%CI			p
Age	1,009	0,991	-	1,027	0,348					
NLR 3.5 Cut Off	5,475	2,921	-	10,263	0,000	4,787	2,515	-	9,111	0,000
ECOG-PS	1,538	0,743	-	3,183	0,246					
R-IPI	1,225	0,934		1,606	0,143					
NCCN-IPI	1,546	1,110	-	2,153	0,010					
Ann Arbor Stage	2,130	1,086	-	4,177	0,028					
B Semptoms	1,168	0,662	-	2,062	0,592					
Bone marrow involvement	1,219	0,647	-	2,294	0,540					
LDH	1,699	1,125	-	2,566	0,012					
Extranodal involvement	1,024	0,730	-	1,435	0,891					
Bulky disease	0,905	0,454	-	1,803	0,777					
Response	2,697	1,952	-	3,725	0,000					
Cox Regresyon (Forward LR)										

PFS: Progression-Free Survival; HR: hazard ratio; CI: Confidence Interval; NLR: neutrophil to lymphocyte ratio; ECOG-PS: Eastern Cooperative Oncology Group performance score; R-IPI: Revised-International Prognostic Index; NCCN-IPI: National Comprehensive Cancer Network-International Prognostic Index LDH: lactate dehydrogenase

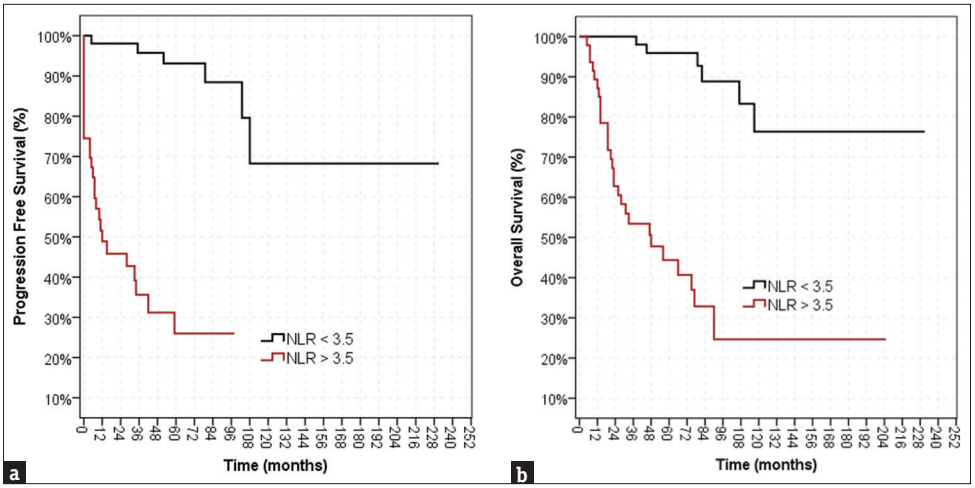

Figure 2: Kaplan–Meier survival analysis of Progression-Free Survival (a) and Overall suS (b) according to neutrophil to lymphocyte ratio (NLR)

Table 4: Univariate and Multivariate Cox regression analysis for OS

Factor	Univariate analysis					Multivariate analysis				
	HR	95% CI			p	HR	95% CI			p
Age	1,030	1,005	-	1,056	0,017	1,052	1,021	-	1,083	0,001
Sex	1,233	0,612	-	2,482	0,557					
NLR 3.5 Cut Off	11,227	4,478	-	28,149	0,000	5,457	1,885	-	15,795	0,002
ECOG-PS	3,560	1,665	-	7,614	0,001					
R-IPI	1,678	1,188	-	2,370	0,003					
NCCN-IPI	1,997	1,319	-	3,025	0,001					
Ann Arbor Stage	3,662	1,284	-	10,438	0,015					
B Semptoms	1,115	0,543	-	2,289	0,766					
Bone marrow involvement	1,011	0,440	-	2,323	0,979					
LDH	2,107	1,246	-	3,565	0,005					
Extranodal involvement	1,051	0,673	-	1,641	0,828					
Bulky disease	0,548	0,193	-	1,558	0,259					
Response	2,539	1,900	-	3,393	0,000	2,126	1,494	-	3,025	0,000
Relaps status	10,102	3,080	-	33,131	0,000	5,656	1,657	-	19,309	0,006

Cox Regresyon (Forward LR) OS: Overall Survival; HR: hazard ratio; CI: Confidence Interval; NLR: neutrophil to lymphocyte ratio; ECOG-PS: Eastern Cooperative Oncology Group performance score; R-IPI: Revised-International Prognostic Index; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index LDH: lactate dehydrogenase

significantly ($P < 0.000$) shorter than in the group with NLR < 3.5 (185 months) [Figure 2a].

On univariate analysis, age ($P = 0.017$), NLR ($P = 0.000$), ECOG-PS ($P = 0.001$), R-IPI ($P = 0.003$), NCCN-IPI scores ($P = 0.001$), Ann Arbor Stage ($P = 0.015$), LDH level ($P = 0.005$), treatment response ($P = 0.000$), and relapse status were significantly associated with OS. In multivariate analysis, age ($P = 0.001$), NLR 3.5 cut-off ($P = 0.002$), treatment response ($P = 0.000$), and relapse status ($P = 0.0006$) had independent effects on OS [Table 4]. The median OS for NLR ≥ 3.5 and < 3.5 were 79.2 months (95% CI 51.6-106.8) and 197.8 months (95% CI 173.2-222.5), respectively [Figure 2b]. NLR ≥ 3.5 was associated with a worse OS than NLR < 3,5 ($P = 0.000$).

Discussion

Previous studies show that persistent chronic inflammation can trigger tumorigenesis.[16,19,20] Neutrophils were settled in the tumor microenvironment to stimulate cancer development by secreting various cytokines.[21] Lymphocytes can cause cytotoxic cell death and are well known to play dominant roles in immune defense against cancer cells also NLR reflects the strength of immune responses.[22,23] NLR was an important prognostic factor in patients with solid tumors such as gastric, breast, head and neck, hepatocellular carcinoma, lung, esophageal cancer, and melanoma.[24-30] Although the prognostic role of NLR has been demonstrated in numerous solid tumors, its utility in leukemia and lymphomas remains uncertain. Its prognostic value in DLBCL patients treated with R-CHOP was first demonstrated by Porrata *et al*. in 2010.[31] Followed by Porrata *et al*., two meta-analyses concluded that NLR is an important predictor factor for poor OS and PFS in DLBCL and also insisted that NLR can be used as an independent risk factor for DLBCL.[31-33] In a study of 530 patients conducted in 2019, no statistical difference was found between NLR with OS and PFS.[34] In contrast to this study, we found that higher NLR was associated with worse PFS and OS, this finding is also similar to most previous studies in the literature.[31-34]

When analyzing the correlation with other clinical parameters, the group with high NLR was observed to have low ECOG-PS, high LDH levels, and an advanced stage of the disease. There was no correlation found with age, gender, bone marrow involvement, extranodal disease, B symptoms, and presence of bulky disease. Literature shows that there are differences in studies analyzing similar parameters.[32,33,35] This can be explained by the limited sample size and the usage of different NLR cut-off values. Different studies have shown that the NLR cut-off values (lowest 2.11, highest 6) varied.[36,37] In our study, we determined the NLR cut-off value as 3.5 by the studies of Porrata *et al*. and Park *et al*.[31,36]

The analysis of the correlation between NLR and R-IPI and NCCN-IPI scores, both of which have prognostic value among DLBCL patients, showed a significant increase in R-IPI and NCCN-IPI scores for a group with NLR ≥ 3.5. Annibali *et al*.[35] conducted a study including 505 DLBCL patients enrolled in an Italian real-world database and found that NLR is an independent prognostic factor that can be used to classify patients into low or intermediate IPI groups (IPI < 3).

Treatment responses were evaluated, and results were similar to those from the study by Demir *et al*.[38] A higher amount of (98.1%) patients with low NLR achieved a CR in our study, also patients with low NLR had lower recurrence rates and mortality. According to the multivariate analysis, NLR was an independent prognostic factor for both PFS and OS.

As a result; this study confirmed that NLR can be used as an inexpensive and easily interpretable prognostic marker in DLBCL patients and may provide guidance for individualisation of treatment, especially by early detection of patients with poor prognosis. However, our study had some limitations such as being retrospective, had a small patients series in single center. Therefore, further prospective, multicentre studies with larger patient series are needed to prove that NLR was an independent prognostic marker.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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