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Original Research

Can the Prognosis of Diffuse Large B-Cell Lymphoma be Predicted by a Simple CBC Count?

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ABSTRACT
Objective: In this study, we aimed to develop a new prognostic model using the neutrophil-to-lymphocyte ratio (NLR) and defined prognostic indexes to improve the results in patients with diffuse large B-cell lymphoma (DLBCL).
Methods: The data of 340 newly diagnosed patients with DLBCL, who underwent at least two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), were evaluated retrospectively. A receiver operating characteristic (ROC) curve analysis was used to determine the NLR cut-off value. The NLR cut-off value was 4.76. In the study, a total of 231 patients (67.9%) were in the low NLR ≤4.76 group, while 109 patients (32.1%) were in the high NLR (NLR >4.76) group.
Results: The 5-year overall survival (OS) was 37.1%, and 78.9% in the high NLR group, and low NLR group, respectively. A high pre-treatment NLR was associated with a worse OS and progression-free survival (PFS) (both p<0.001, respectively). In the multivariate analysis, a high pre-treatment NLR and a high National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) status were found to be as an independent risk factors of poor OS (hazard ratio [HR]= 2.28; 95% confidence interval [CI]= 1.51-3.45; p= 0.001; HR= 5.59; 95% CI= 3.22-9.70; p= 0.001, respectively) and PFS.
Conclusion: The study found that a high NLR was associated with a poor treatment response, poor PFS, and OS. In view of these data, we believe that the creation of an inflammation-based cumulative prognostic score system (IBCPSS), by adding NLR among the factors whose prognostic importance has been proven in DLBCL, can especially shed light on the early diagnosis of patients with a poor prognosis, aggressive treatment decision, and individualization of treatment.
Keywords: Diffuse large B-cell lymphoma, score system, neutrophil-to-lymphocyte ratio, prognosis

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas, and it accounts for 40% of all lymphomas (1). As a result of adding rituximab to a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), a dramatic improvement was seen in the treatment outcome, progression-free survival (PFS), and overall survival (OS) (2). However, resistance to the initial treatment regime and post-treatment recurrence are seen in over 30% of DLBCL patients (3). The IPI is a risk classification system commonly used to predict the outcome and choose the best therapeutic treatment in patients with aggressive lymphoma (4). However, IPI is insufficient, particularly in the identification of patients with a poor prognosis and low probability of survival, as it was established in the pre-ritumixab era. Therefore, IPI capacity enhancement studies have been carried out, and IPI variants such as revised IPI (R-IPI) (5) and, the National Comprehensive Cancer Network-IPI (NCCN-IPI) (6) have been developed in risk classification. Unfortunately, these models are also insufficient to identify patients with a poor prognosis who cannot benefit from the R-CHOP treatment. Additionally, it is known that an adequate survival benefit could still not be reached in a significant number of patients with DLBCL despite the addition of rituximab to the CHOP treatment (7). Therefore, studies are still underway to identify new markers for the prognosis in patients with DLBCL receiving R-CHOP therapy. In addition to the conventional prognostic factors in the literature, the importance of some inflammatory aspects in the prognosis of DLBCL has been investigated. A high C-reactive protein (CRP) level (8), lower absolute lymphocyte-to-monocyte ratio (LMR) (9), high Beta-2 microglobulin level (B2-MG) (10), and a high absolute neutrophil count (ANC) (11) were associated with poor prognosis, while a high absolute lymphocyte count (ALC) (12) was defined as a positive prognostic factor in response to treatment. Prognostic importance of the plasma fibrinogen level in DLBCL could not be shown (13). It was reported that there was a close link between the development of lymphoma, and chronic inflammation, immunodeficiency, and infections. In addition, the role of immune response and abnormal inflammatory response in predicting the clinical course in patients has also been shown in some studies (14). The neutrophil-to-lymphocyte ratio (NLR) is an important parameter that indicates a systemic inflammatory response, and provides an advantage in the determination of prognosis when compared to ALC and ANC. It has been proven that it could be used as an important predictor for survival estimation in many cancers (15, 16). It was first reported by Porrata et al. (17) as an independent prognostic factor in patients with DLBCL treated with R-CHOP. The prognostic significance of NLR

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in DLBCL was then demonstrated in a limited number of studies (18, 19). The aim of this study was to evaluate the prognostic and predictive value of NLR in patients with DLBCL treated with R-CHOP as the first-line therapy together with clinical and laboratory parameters to make a new model to improve the well-known prognostic index.

METHODS

Patients

The data of 340 newly diagnosed patients with DLBCL, who were followed up in the Gaziantep University of Hematology Department between 2004 and 2018, and underwent at least two cycles of R-CHOP in the first-line treatment, were evaluated retrospectively. Patients who did not receive R-CHOP as the first-line therapy and had an active infection at the time of diagnosis were excluded from the study. The study was approved by Gaziantep University Medical Faculty Medical Ethics Committee, which was dated 23.01.2019 and numbered 2019/40, and a written informed consent was obtained.

Clinical Data

Patients' clinical parameters (age, gender, Eastern Cooperative Oncology Group performance score [ECOG-PS], B symptoms, bulky disease, stage, extranodal disease), laboratory parameters (serum lactate dehydrogenase [LDH], B2-MG, CRP levels and albumin value, erythrocyte sedimentation rates [ESR], NLR, treatment response, and risk classification (IPI, R-IPI, NCCN-IPI) were carefully recorded at the time of diagnosis from the patient files. The neutrophil, and lymphocyte counts were determined from routine complete blood count obtained at the time of diagnosis of NHL using Sysmex automated hematology analyzers (Sysmex XN 9000, Erlangen, Germany). The cut-off value for laboratory parameters was determined on the basis of the upper/lower limit of the local laboratory, and the cut-off point for NLR was found to be 4.76 ($p<0.001$; AUC= 0.686; Sensitivity= 56.14% [95% CI= 46.50-65.40]; Specificity= 80.09% [95% CI= 74.30-85.10] using the receiver operating characteristic (ROC) analysis.

Statistical Analysis

A chi-square test was performed in the comparison of characteristics of the high and low NLR groups. The Kaplan-Meier method was used to calculate PFS and OS, and a log-rank test was used to compare PFS and OS lifespan according to the NLR. Univariate and multivariate survival analyses were calculated using the Cox' regression model. A p-value <0.05 was considered statistically significant. Count, percentage, mean, and standard deviation values of the data were calculated. The Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp.; Armonk, NY, USA) program was used in the analysis of all data.

RESULTS

Associations of NLR with Clinical Characteristics

Of the 340 patients included in the study, 154 were females, 186 were males, and the mean age was 52.71±16.85 years. Characteristics of patients in the high and low NLR groups are summarized in Table 1. A total of 114 (33.5%) of the patients included in the study was died due to refractory/relapse lymphoma. There were 231 (67.9%) and 109 (32.1%) patients in the high and low NLR groups, respectively. There were significant differences between the high and low NLR groups in terms of patient characteristics. When comparing the patients in the high NLR group with those in the low NLR group, the high NLR group was significantly correlated with an advanced age (>60 years; 48.7% vs. 51.3%, $p<0.001$), poor performance status (ECOG-PS 2-3, 73.6% vs. 26.4%; $p<0.001$), high LDH (normal LDH >3, 64.3% vs. 35.7%, $p<0.001$), high ESR (ESR >40, 44.6% vs. 55.4%, $p<0.001$), high B2-MG level (B2-MG ≥3.5, 55.5% vs. 44.5%, $p<0.001$), high CRP level (CRP >5, 40.0% vs. 60.0%, $p<0.001$), low albumin level (albumin <4.5, 34.9% vs. 65.1%, $p<0.001$), and the presence of extranodal sites involvement (extranodal disease, 36.9% vs. 63.1%, $p<0.001$). The NLR was also relevant to bulky disease and B symptoms (both $p<0.001$). There was no significant difference between the high and low NLR groups in terms of the patients' stage at the time of diagnosis ($p=0.636$). Patients in the high NLR group were significantly correlated with a high IPI, R-IPI, and NCCN-IPI (high-intermediate to high IPI, 50.0% vs. 50.0%, $p<0.001$; poor R-IPI, 49.0% vs. 51.0%, $p<0.001$; high-intermediate to high NCCN-IPI, 46.7% vs. 53.3%, $p<0.001$).

Treatment Response

The treatment response of patients who received R-CHOP as the first-line therapy was grouped as complete response (CR), and partial response, stable disease, no response, and progressive disease. A 25% dose reduction was made in the treatment regime of a limited number of patients over the age of 75, excluding rituximab. CR rate was lower in the high NLR group as compared to the low NLR group (24.6% vs. 75.4%; $p<0.001$; Table 1).

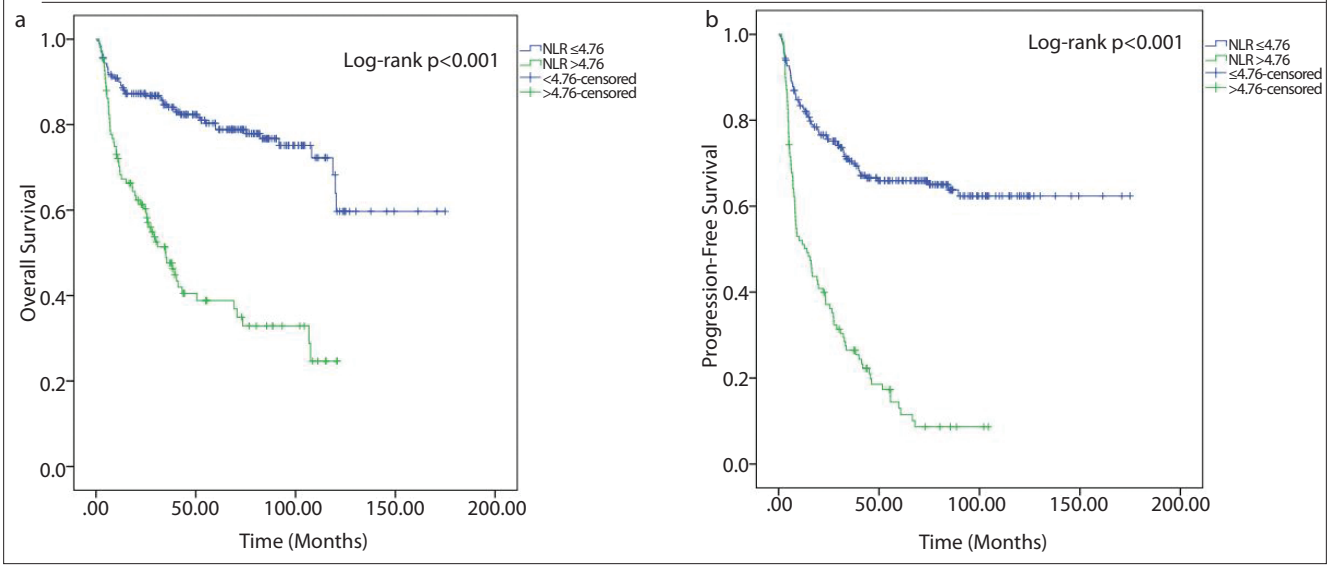
Survival

The median follow-up time was 38.5 months (range, 0.2-170 months). The 5-year OS and 5-year PFS rates were 66.4% and 48.5%, respectively. The 5-year OS rate was 37.1%, and 78.9% in the high NLR group, and low NLR group, respectively. A high pre-treatment NLR was found to be associated with poor OS (the mean OS for NLR >4.76: 53.95±5.05; 95% CI= 44.03-63.87; $p<0.001$; Figure 1a). The 5-year PFS rate, on the other hand, was 13.0%, and 65.5% in the high NLR group, and low NLR group, respectively. A high pre-treatment NLR was associated with poor PFS (the mean PFS for NLR >4.76: 26.82±2.98; 95% CI= 20.97-32.67; $p<0.001$; Figure 1b).

The Cox regression model was used to determine the important variables in the PFS and OS times. In the Cox regression analysis, variables with a high level of correlation between each other (age, ECOG, IPI, R-IPI) were checked for their Variance inflation factor coefficient and excluded from the analysis. On univariate analysis, an elevated LDH, extranodal sites involvement, and high NLR and high NCCN-IPI scores were significantly associated with poor OS (HR=1.97, 95% CI=1.23 - 3.14, p=0.004; HR= 2.34, 95% CI=1.52 - 3.58, p=0.001; HR=3.88, 95% CI=2.67 - 5.65, p=0.001; HR=8.12, 95% CI=4.90 - 13.45, p=0.001, respectively). In a multivariate analysis, only pre-treatment NLR and NCCN-IPI remained as independent prognostic factors (HR=2.28, 95% CI=1.51 - 3.45, p=0.001; HR=5.59, 95% CI=3.22 - 9.70, p=0.001, respectively; Table 2).

Figure 1. a, b. Survival (a) OS and (b) PFS According to NLR

NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PFS: progression-free survival



A high LDH, extranodal disease, high NLR, and high NCCN-IPI scores at the time of diagnosis were associated with a poor PFS in the univariate analysis (HR=1.78, 95% CI=1.23 - 2.58, p=0.002; HR=2.08, 95% CI=1.49 - 2.92, p=0.001; HR=4.18, 95% CI=3.06 - 5.69, p= 0.001; HR=3.05, 95% CI=2.21 - 4.21, p=0.001, respectively; Table 3). A high pre-treatment LDH, extranodal disease, high NLR, and high NCCN-IPI status were found to be also significant in the multivariate analysis, and as independent risk factors for poor PFS (HR=1.87, 95% CI=1.23 - 2.85, p=0.003; HR=1.52, 95% CI=1.07 - 2.17, p=0.019; HR=2.93, 95% CI=2.08 - 4.11, p=0.001; HR=1.79, 95% CI=1.24 - 2.59, p=0.002, respectively; Table 3).

DISCUSSION

In the literature, many studies have shown that there is a correlation between a pre-treatment NLR and survival in solid tumors (20, 21). There are a limited number of studies that examine the prognostic importance of NLR in DLBCL, which is the most commonly seen lymphoma subtype among hematologic malignancies. Similar to the studies in the literature, our study showed that a high pre-treatment NLR is associated with a high LDH level, extranodal sites involvement, and poor IPI and NCCN-IPI (18, 22). A significant correlation was demonstrated between a high NLR and poor prognostic indicators such as an advanced age, poor ECOG-PS status, bulky disease and B symptoms, ESR, CRP, B2-MG, and albumin values, which are the indicators of a systemic inflammatory response. Prognostic risk indexes, IPI in the pre-rituximab era, and R-IPI and NCCN-IPI after rituximab were found to be significantly associated with NLR. Only NCCN-IPI and NLR were independent risk factors for survival in the multivariate analysis, while the LDH, extranodal sites involvement, NLR, and NCCN-IPI were found to be independent risk factors in PFS. In this study, the 5-year OS was 37.1% in the high NLR group. Similarly, in the study by SI Go et al. (19) using NCCN-IPI, the 5-year OS was 30%, and in another study, it was 46% (23). Different results in similar studies might be associated with the absence of a specific cut-off value for NLR. In our study, the cut-off value for the pre-treatment NLR was determined as 4.76 using the ROC analysis. The cut-off value varies between 3.0 and 6.0 in different studies (9, 23, 24). There is no ideal method for determining the NLR cut-off value. This limits the value of our study as it did in similar previous studies. However, it seems possible to increase the prognostic value of NLR by determining a standardized cut-off value and evaluating the NLR together with parameters whose prognostic importance has been proven to make an individualized risk classification. Despite the different results, the effect of NLR on survival has been reported in many studies (17, 24). The potential mechanism is still not exactly known. However, some possible mechanisms have been defined. First, circulating interleukin (IL)-17 and IL-18 levels were found to be elevated in the serum of patients with a high NLR (25). These proinflammatory cytokines have been shown to play a role in the continuity of the tumor microenvironment and the aggressive course of the tumor (26). Second, a high NLR reflects increased neutrophil count, and a high neutrophil count is associated with the vascular endothelial growth factor synthesis, which plays a vital role in tumor development and angiogenesis (25). The third potential mechanism in the correlation between a high NLR and survival is that a high NLR causes suppression of the ALC. Lymphocytes create a host immune response against malignancies (22). In some immunologic studies performed on solid tumors, it was shown that an increased ANC in the peripheral blood are actually CD11, CD33, and CD15 positive myeloid-derived suppressor cells (MDSC), which play a role in the development and progression of cancer by suppressing the human immune system (lymphopenia). Also, tumor-associated neutrophils (TANs) derived from MDSC have an important role in the tumor proliferation and metastasis. There are two different phenotypes of TANs: protumorogenic and anti-tumorogenic. An increase in tumorogenic TANs leads to a high NLR with T-cytotoxic suppression (27, 28). In this context, it is evident that differential diagnosis of these two phe-

Table 1. Patients' characteristics and treatment response

		NLR		
		≤4.76	>4.76	p
Age	≤60	170 (76.9)	51 (23.1)	<0.001
	>60	61 (51.3)	58 (48.7)	
Sex	Male	125 (67.2)	61 (32.8)	0.816
	Female	106 (68.8)	48 (31.2)	
ECOG - PS	0 - 1	212 (79.1)	56 (20.9)	<0.001
	2 - 3	19 (26.4)	53 (73.6)	
B symptoms	No	184 (81.1)	43 (18.9)	<0.001
	Yes	47 (41.6)	66 (58.4)	
Bulky disease	No	177 (79.4)	46 (20.6)	<0.001
	Yes	54 (46.6)	62 (53.4)	
Stage	1 - 2	89 (66.4)	45 (33.6)	0.636
	3 - 4	142 (68.9)	64 (31.1)	
Extranodal disease	No	101 (75.4)	33 (24.6)	0.024
	Yes	130 (63.1)	76 (36.9)	
LDH	≤1	130 (83.3)	26 (16.7)	<0.001
	<1 to ≤3	76 (66.7)	38 (33.3)	
	>3	25 (35.7)	45 (64.3)	
Response to treatment	CR	190 (75.4)	62 (24.6)	<0.001
	Other	41 (46.6)	47 (53.4)	
IPI	Low to low-intermediate	159 (81.1)	37 (18.9)	<0.001
	High-intermediate to high	72 (50.0)	72 (50.0)	
R-IPI	Very good	37 (90.2)	4 (9.8)	<0.001
	Good	118 (78.1)	33 (21.9)	
	Poor	75 (51.0)	72 (49.0)	
NCCN-IPI	Low to low-intermediate	143 (81.7)	32 (18.3)	<0.001
	High-intermediate to high	88 (53.3)	77 (46.7)	
ESR	<40	154 (76.6)	47 (23.4)	<0.001
	≥40	77 (55.4)	62 (44.6)	
B2-MG	0 - 3.4	174 (82.1)	38 (17.9)	<0.001
	≥3.5	57 (44.5)	71 (55.5)	
CRP	0 - 5	87 (87.0)	13 (13.0)	<0.001
	>5	144 (60.0)	96 (40.0)	
Albumin	0 - 4.4	190 (65.1)	102 (34.9)	0.004
	>4.5	41 (85.4)	7 (14.6)	

ECOG-PS: Eastern Cooperative Oncology Group performance score; LDH: lactate dehydrogenase; CR: complete remission; IPI: International Prognostic Index; R-IPI: Revised-International Prognostic Index; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index; ESR: erythrocyte sedimentation rate; B2-MG: Beta-2 microglobulin; CR: C-reactive protein

Table 2. Univariate and multivariate analysis for OS outcomes

	Univariate Analysis		Multivariate Analysis	
	p	HR (95.0% CI)	p	HR (95.0% CI)
Elevated LDH	0.004	1.97 (1.23–3.14)	0.057	1.65 (0.98–2.78)
Ann Arbor stage	0.156	1.32 (0.89–1.96)	0.302	1.23 (0.83–1.82)
Extranodal disease	0.001	2.34 (1.52–3.58)	0.528	1.15 (0.73–1.81)
NLR (≤4.76 vs. >4.76)	0.001	3.88 (2.67–5.65)	0.001	2.28 (1.51–3.45)
NCCN-IPI scores	0.001	8.12 (4.90–13.45)	0.001	5.59 (3.22–9.70)

LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index; OS: overall survival

Table 3. Univariate and multivariate analysis for PFS outcomes

	Univariate Analysis		Multivariate Analysis	
	p	HR (95.0% CI)	p	HR (95.0% CI)
Elevated LDH	0.002	1.78 (1.23–2.58)	0.003	1.87 (1.23–2.85)
Ann Arbor stage	0.842	0.96 (0.71–1.31)	0.771	1.04 (0.76–1.43)
Extranodal disease	0.001	2.08 (1.49–2.92)	0.019	1.52 (1.07–2.17)
NLR (≤ 4.76 vs > 4.76)	0.001	4.18 (3.06–5.69)	0.001	2.93 (2.08–4.11)
NCCN-IPI scores	0.001	3.05 (2.21–4.21)	0.002	1.79 (1.24–2.59)

LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; NCCN-IPI: National Comprehensive Cancer Network- International Prognostic Index; PFS: progression-free survival

notypes cannot be performed by the neutrophil count in the peripheral blood. In addition, a detection of MDSC and TANs in the peripheral blood is a costly method and not practical. It appears to be more appropriate to use NLR as an indicator of proinflammatory state until a new parameter is defined.

It was reported in different studies that ESR (29), CRP (7), and B2-MG (30) can be used to determine the prognosis in DLBCL. This study also showed that the ESR, B2-MG, CRP levels, and the albumin value, which are among the parameters that show a systemic inflammatory response, are associated with high NLR. The search for identifying new prognostic parameters in DLBCL continues. In recent years, the investigation of the prognostic significance of NLR in DLBCL has been a popular study topic among researchers. Despite the different cut-off values, a high pre-treatment NLR was found to be associated with poor survival since it indicates a probable tumor-associated neutrophilia, that is, reflecting a systemic inflammatory response (19, 20). DLBCL is the most commonly seen hematologic malignancy, and the definition of resistance to R-CHOP treatment in a significant number of patients indicates the need for a new risk classification index. In the present study, a pre-treatment NLR was examined together with many proinflammatory parameters, and its effect on OS and PFS was determined. In view of these data, it is believed that the creation of an inflammation-based cumulative prognostic score system (IBCPSS, a new model for risk stratification), by adding NLR in the factors whose prognostic importance has been proven in DLBCL along with ESR, B2-MG, CRP, and albumin levels, which are among the parameters that reflect the systemic inflammatory response, can especially shed light on the early diagnosis of patients with poor prognosis, aggressive treatment decision, and particularly on the individualization of treatment.

As a result, NLR was demonstrated as a strong prognostic marker in patients with DLBCL treated with R-CHOP as the first-line therapy in this study. Also, it was shown that the degree of the systemic inflammatory response plays a major role in the clinical course, treatment response, and predicting prognosis. It seems possible that a new risk scoring system (IBCPSS), which can be established by adapting the inflammation parameters and NLR to the well-known risk classification index, can be used as a more potent prognostic index in the individualized treatment decision in the near future.

Ethics Committee Approval: The study was approved by Gaziantep University Medical Faculty Medical Ethics Committee (dated 23.01.2019 and numbered 2019/40).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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