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The Association of NLR and MPV with Treatment Responses, Disease Stages, and International Prognostic Index Scores in Diffuse Large B-Cell Lymphoma

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ABSTRACT

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. International Prognostic Index (IPI) is the most commonly used scoring system predicting the prognosis. In this study, we aimed to investigate the association of Neutrophil/Lymphocyte Ratio (NLR) and Mean Platelet Volume (MPV) with IPI score, treatment responses, and disease stage.

A total of 113 DLBCL patients who received R-CHOP treatment were recruited for this study. Demographic data, disease stages according to the Ann Arbor staging system, IPI scores, treatment methods, treatment responses, complete blood counts, and biochemical tests of the patients were retrospectively evaluated.

Elevated NLR had statistically significant correlation with disease stage and IPI score (p=0.001 and p=0.006, respectively). However, the NLR had no statistically significant correlation with the interim-treatment and post-treatment responses (p=0.187, and p=0.96, respectively). MPV showed no significant relationship with disease stages (p=0.56), IPI scores (p=0.188), interim-treatment and post-treatment responses (p=0.122, and p=0.239).

In conclusion, NLR was associated with IPI score and disease stage. This suggests that NLR, a cheap and easy investigation, may be used to obtain information about the prognosis.

Key Words: Diffuse Large B-Cell Lymphoma, Neutrophil/Lymphocyte Ratio, Mean Platelet Volume, Prognosis

Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for 25% to 30% of adult non-Hodgkin lymphomas (1). A strong correlation is observed between the prognosis of DLBCL and International Prognostic Index (IPI) score. The IPI score is currently used for determining the prognosis of DLBCL (2, 3). Besides, low lymphocyte count in the diagnosis or in the first relapse of DLBCL is a poor prognostic factor for survival (4-7). An elevated neutrophil count at diagnosis has been associated with poor prognosis in solid tumors (8).

On the other hand, many studies have shown that the Neutrophil/Lymphocyte Ratio (NLR) may be a prognostic indicator for survival in solid tumors and DLBCL (9-13). In two studies, it has been shown that the low Mean Platelet Value (MPV) at diagnosis was found to be associated with a decreased survival rate in DLBCL (14, 15). However, increased MPV has been shown to be related to better survival rates in cancer patients (16, 17).

In this study, we aimed to investigate the association of Neutrophil/Lymphocyte Ratio (NLR) and Mean Platelet Volume (MPV) with the IPI score, treatment responses, and disease stage.

Materials and Methods

A total of 113 patients who were diagnosed with DLBCL and treated with 6-8 cycles R-CHOP in our clinic between 2010-2018 were included in this study. Demographic data, disease stages according to the Ann Arbor staging system, IPI scores, treatment methods, treatment responses, complete blood counts, and biochemical tests of the patients were retrospectively evaluated. Response evaluation was performed according to Lugano response criteria. Patients who did not have a complete blood count at the time of diagnosis, IPI score unknown, active infection, patients who did not complete treatment, patients lost during treatment, patients who did not comply with R-CHOP treatment were not included in the study.

In this study, the descriptive statistics of the

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Table 1. Participant features

		n (%)	Mean	Min-Max	Std.Deviation
Age		113	54.7	18-88	15.44
Gender	Male	62 (%55)			
	Female	51 (%45)			
Stage	Stage 1	10 (%9)			
	Stage 2	24 (%21)			
	Stage 3	41 (%36)			
	Stage 4	38 (%34)			
	Low stage	34 (%30)			
	High stage	79 (%70)			
IPI	IPI 0	4 (%4)			
	IPI 1	15 (%13)			
	IPI 2	31 (%27)			
	IPI 3	34 (%30)			
	IPI 4	20 (%18)			
	IPI 5	9 (%8)			
	Low IPI	51 (%45)			
	High IPI	62 (%55)			
Leukocytes count (/mm^3)		113	7.600	600-23.700	3.350
Neutrophil count (/mm^3)		113	5.200	200-19.300	2.940
Lymphocyte count (/mm^3)		113	1.600	100-4000	890
NLR		113	6.1	0.25-109	11.91
Hemoglobin (g/dl)		113	12.3	5.4-16.5	2.27
Platelet count (/mm^3)		113	279.000	25.000-698.000	114.59
MPV (fl)		112	9.7	5.1-108	9.50
Sedimentation (mm/h)		104	35.2	1-111	24.40
CRP (mg/dl)		107	42.6	1-231	43.39

continuous variables were expressed as mean, standard deviation, minimum, and maximum, while the descriptive statistics of the categorical variables were expressed as number and percentage. Complete blood count was performed in the same laboratory with an automated device. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The threshold values of NLR and MPV were determined by the ROC analysis. The association of NLR and MPV with IPI scores and treatment responses were evaluated by the Chi-Square test. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, version 24, IBM, Armonk, New York 10504, NY, USA). Approval was received from the Noninvasive Clinical Research Ethics Board at Van Yüzüncü Yıl University with the date 06.06.2018 and approval number 04.

Results

A total of 113 patients were recruited for this study. Study participants included 51 (45.2%) women and 62 (54.8%) men. The mean age of patients was 54.68 years (min=18 and max=88). According to the Ann Arbor staging, 10 patients (8.9%) were in Stage-I, 24 patients (21.2%) in Stage-II, 41 patients (36.3%) in Stage-III, and 38 patients (33.6%) in Stage-IV. We merged stages I and II as "low stage," and stages III and IV as "high stage." Thirty-four patients (30.1%) were present in the low-stage group and 79 patients (69.9%) in the high-stage group. On the other hand, according to the IPI scoring, four patients (3.5%) were scored as IPI-0, 15 patients (13.2%) as IPI-1, 31 patients (27.5%) as IPI-2, 34 patients (30.1%) as IPI-3, 20 patients (17.7%) as IPI-4, and 9 patients (8%) as IPI-5. IPI scores 0, 1, and 2 were classified as "low IPI score," and IPI scores 3, 4, and 5 were classified as "high IPI score." Fifty-one patients (45.1%) were in the low IPI score group, while 62 patients (54.9%) were in the high IPI score group (Table 1).

In the interim-treatment response assessment, it was detected that 59 (52.2%) patients had a complete response (CR), 42 (37.2%) patients had a partial response (PR), and the remaining 12 (10.6%) patients had stable disease (SD). Additionally, it was detected in the post-treatment response assessment that 86 (76.1%) patients had CR, 9 (8%) patients had PR, and the remaining 18 (15.9%) patients had SD. The

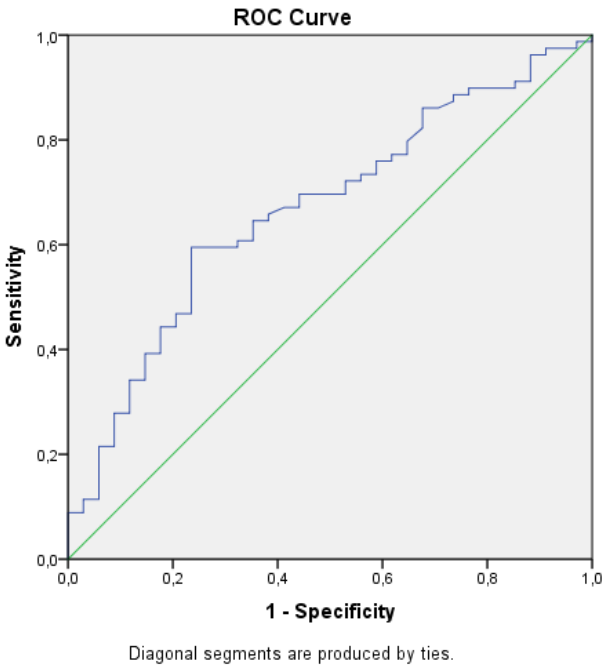

Fig. 1. Receiver operating characteristic curve (ROC) and area under the curve (AUC) for NLR at diagnosis (AUC=0.668, P=0.005; 60.0% sensitivity and 76.5% specificity). AUC = area under the curve, NLR = neutrophil lymphocyte ratio, ROC = receiver operating characteristic curve

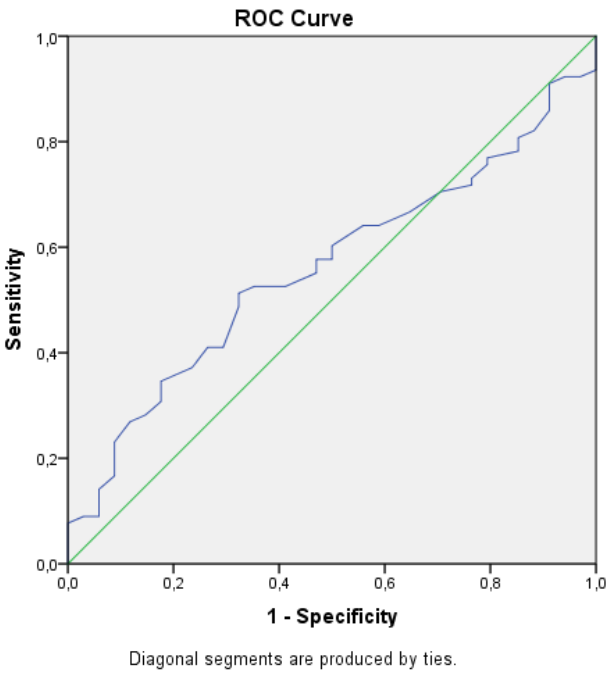

Fig. 2. Receiver operating characteristic curve (ROC) and area under the curve (AUC) for NLR at diagnosis (AUC=0.560, P=0.005; 51.0% sensitivity and 67.6% specificity).AUC=area under the curve, NLR= neutrophillymphocyte ratio, ROC = receiver operating characteristic curve

threshold value of NLR was found as 3.235 using ROC analysis (Figure 1). On the other hand, the threshold value of MPV was found as 9 fl using ROC analysis (Figure 2).

The NLR was over 3.235 in 21.5% of the low-staged patients and 59.5% of the high-staged patients (p=0.001). It was also over 3.235 in 33.3% of the low IPI-scored patients and 61.3% of the high IPI-scored patients (p=0.006). The elevated NLR (>3.235) had a statistically significant correlation with high stage and high IPI score (p=0.001 and p= 0.006, respectively). However, it had no significant correlation with the interim-treatment and post-treatment responses (p=0.187, and p= 0.96, respectively).

The NLR was over 3.235 in 43% of the DLBCL survivors and 72.7% of those who died (p=0.012). NLR at diagnosis was higher in the deceased group compared to the survivors (p= 0.012). On the other hand, the NLR showed significant positive correlations with sedimentation rate (p= 0.029) and CRP (p= 0.013) with a negative correlation with hemoglobin (p=0.003).

MPV had no statistically significant association with stage (low vs. high) (p=0.56), IPI score status (low vs. high) (p=0.188), interim-treatment response assessment (p=0.122), post-treatment response assessment (p=0.239), and mortality status (p=0.311).

Similarly, no correlation was found between NLR and MPV (p=0.51).

There was a negative correlation between hemoglobin levels and disease stage (p=0.000), IPI score (p=0.001) and NLR (p=0.003). Conversely, increased CRP values had a positive correlation with advanced disease stage (p=0.000), high IPI score (p=0.001) and elevated NLR (p=0.013). Finally, increased sedimentation values had a positive correlation with advanced disease stage (p=0.006), increased rate of non-responders in the interim-treatment response assessment (p=0.039), and the number of deceased patients (p=0.03).

Discussion

Although the NLR and MPV have prognostic significance in many cancer types, a definite threshold value is still unknown. In this study, the threshold levels of NLR and MPV were detected as 3.235 and 9 fl, respectively. We also found that elevated NLR was associated with high IPI scores and advanced disease stage. In addition, the NLR at diagnosis was significantly higher in deceased patients compared to the survivors. On the other hand, it was detected that MPV had no statistically significant relationship with IPI scores, disease stage, and treatment responses. It was also detected that hemoglobin had a negative correlation with NLR and IPI scores. There was a

positive correlation between increased CRP, advanced disease stage, high IPI score, and elevated NLR. An increase in sedimentation rate was associated with an advanced disease stage and increased rate of non-responders in interim-treatment response assessment. The sedimentation rate at diagnosis was significantly higher in deceased patients compared to survivors.

Porrata et al. showed NLR to be an independent prognostic factor for progression-free survival (PFS) and overall survival (OS). The patients with an NLR of <3.5 at diagnosis experienced an OS and PFS compared with those patients with an NLR >3.5 at diagnosis (13). Higher NLR was also associated with B-symptoms ($p<0.003$), Stage III/IV ($p<0.002$), and with higher LDH levels ($p<0.0001$). Additionally, a correlation was detected between elevated NLR and high IPI scores (13). Similarly, we detected higher IPI scores and advanced disease stage in patients with NLR >3.235.

In a study where the NLR cut off was determined as 2.915 in DLBCL patients, it was shown that NLR at diagnosis was an independent prognostic marker for OS and PFS. OS and PFS were longer in patients with NLR <2.915 (2). In another study, the NLR cut off value was accepted as 4.35 in patients with DLBCL. The 5-year PFS and OS was found to be significantly longer in patients with NLR <4.35 than patients having an NLR of >4.35 (3). In our study, the association of NLR and MPV values with survival rate could not be evaluated because of the relatively low follow-up time. However, the elevated NLR at the diagnosis in patients who died and the decreased NLR at diagnosis of the living patients suggest that NLR may have a crucial effect on survival.

Matysek et al. detected that increased risk of venous thromboembolism (VTE) was associated with lower overall survival rates in DLBCL patients with low MPV (<10) (14). On the other hand, Zhou et al. detected a relationship between MPV and clinicopathological factors in DLBCL patients who received R-CHOP treatment. Patients with low MPV (≤9.1 fl) were associated with a shorter PFS (2-year PFS rate, 60.6% vs. 84.0%, $p=0.003$) and OS (2-year OS rate, 70.4% vs. 87.9%, $p=0.030$). It was demonstrated that low MPV is an independent prognostic marker of poor outcome in patients with DLBCL (15). We detected the same MPV cutoff value (9 fl) in this study. However, we could not find an association of MPV with disease stage, IPI score, and treatment responses.

In conclusion, NLR was associated with IPI scores and the disease stage in our study. This suggests that NLR, a cheap and easy investigation, may be used to obtain information about prognosis.

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