Pre-treatment neutrophil-lymphocyte and monocyte-lymphocyte ratios give clues about response, survival, and recurrence in diffuse large B-cell lymphoma

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SUMMARY

Background: *Diffuse large B cell lymphoma is a heterogeneous tumor group consisting of large and transformed B cells that makeup 30-40% of all non-Hodgkin lymphoma. Numerous studies point out that initial parameters and post-treatment responses can be used as prognostic factors. We aimed to examine the relationship between diagnosis, clinical and laboratory parameters, treatment response and survival using neutrophil-lymphocyte and monocyte-lymphocyte ratios.* **Methods:** *A total of 80 patients, followed in our hematology clinic between January 2009-2019, were included in the study and were analyzed retrospectively.* **Results:** *The median value of neutrophil- lymphocyte ratio was 3.5 (0.3-50.2) and of monocyte-lymphocyte ratio was 0.3 (0.1-4.8). In the group with neutrophil-lymphocyte ratio ≥ 3.5 response rates was significantly lower and exitus rate and the bulky mass presence were significantly higher compared to the group with > 3.5 values ($p < 0.05$). In the group with monocyte-lymphocyte ratio ≥ 0.30, the exitus rate was significantly higher compared to group with < 0.30 values ($p < 0.05$).* **Conclusion:** *A statistically significant bulky mass presence was demonstrated in the population above the neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio cut off. Although not considered to be sufficient alone, these parameters could be used as prognostic factors in combination with current scoring systems.*

Key words: *Non-Hodgkin lymphoma, Diffuse large B cell lymphoma, Neutrophil-lymphocyte ratio, Monocyte-lymphocyte ratio, Prognosis*

INTRODUCTION

Lymphomas constitute 3% of all cancers and non-Hodgkin lymphoma (NHL) ranks first among all hematological malignancies. Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B-cells that makeup 30-40% of all NHL (1). Its incidence increases with age; median age at diagnosis is 64. It is more common in men and 55% of the patients are male (2, 3). It can occur *de novo* or histologically transformed from indolent lymphomas. The disease typically presents as a rapidly growing nodal or extra-nodal mass associated with systemic symptoms (4).

Clinical parameters such as age, gender, presence of B symptoms, nodal and extra-nodal involvement areas, clinical stage, and serum lactate dehydrogenase (LDH) level in DLBCL have been frequently studied. These variables can affect survival independently from each other or they can be calculated by evaluating several parameters together. The most commonly prognostic index, first defined in 1993 and then revised, is the "International Prognostic Index (IPI)" (5-7). However, these clinical parameters and IPI score are not always sufficient in determining the prognosis (8).

Many studies point out to initial parameters and post-treatment responses for the prognosis. Gene profile analysis, immuno-histochemical studies, PET/CT (Positron emission tomography/computed tomography) and interim PET studies are performed for the detection of new prognostic factors. Because of cheaper and faster results, the effect of peripheral blood findings in determining the prognosis is being investigated and studies involving different clinical parameters such as neutrophil-lymphocyte ratio (NLR), lymphocyte monocyte (LMR) and thrombocyte lymphocyte ratio (TLR) are increasing (9-14).

The literature shows that NLR and monocyte-lymphocyte ratio (MLR) have been used as a negative prognostic factor for many solid tumors (12-14). Similarly, it appears that it is used as a prognostic factor for DLBCL (9-11).

In our study, we aimed to examine the relationship between diagnosis, clinical and laboratory parameters, treatment response and survival using NLR and MLR in our own patient group.

MATERIAL AND METHODS

DLBCL patients who were followed up in our hematology clinic between January 2009 and 2019, aged over 18 years, were included in the study. The data of 80 patients included in the study were analysed retrospectively, cross-sectionally, from the hospital's electronic database and through the scanning of patient files. Our study was approved by the Clinical Research Ethics Committee of our hospital (Decision number 1342 from July 6th 2018). Stages at diagnosis, IPI scores, gender and other demographic data, initial laboratory results and presence of B symptom were recorded. Treatment responses of the patients after four cycles of chemotherapy were checked with PET/CT and their responses were recorded according to Lugano revised response criteria.

STATISTICAL ANALYSIS

In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. Independent sample t-test or Mann-Whitney U test was used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was used when the conditions of chi-square test were not met. Kaplan Meier-Log rank was used for survival analysis. SPSS 22.0 program was used in the analyses.

RESULTS

Out of 80 patients examined, 33 were female (41.3%) and 47 were male (58.8%). The patients were mainly stage IV, 7 were stage I (8.8%), 16 were

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stage II (20%), 19 were stage III (23.8%), and 38 were stage IV (47.5%) disease. The median NLR of the patients was 3.5 (0.3-50.2); the median value of monocyte-lymphocyte ratio was 0.3 (0.1-4.8) (Table 1).

The patients were divided into two groups based on the determined median values and they were compared statistically separately, with the sub-parameters. In terms of demographic characteristics and laboratory results of the patients, the bulky mass presence was significantly higher in the group with NLR ≥ 3.5 than the group with NLR < 3.5 ($p < 0.05$), no significant difference was found between the other parameters (Table 2).

Considering the answers of the patients and their final situation; the response rate in the group with NLR ≥ 3.5 was significantly lower than the group with NLR < 3.5 ($p < 0.05$). In the group with NLR < 3.5 and NLR ≥ 3.5, the relapse rate after response did not differ significantly ($p > 0.05$). The *exitus* rate was significantly higher in the group with NLR ≥ 3.5 than the group with NLR < 3.5 ($p < 0.05$) (Table 3).

The patients were evaluated by dividing into two groups according to the MLR median value of 0.3. While neutrophil and thrombocyte values did not differ significantly (p 0.05) in both groups, hemoglobin and lymphocyte values were significantly lower in the group with MLR ≥ 0.30 than the group with MLR < 0.3 ($p < 0.05$). Neutrophil, monocyte and high LDH were significantly higher in the group with MLR ≥ 0.30 than the group with MLR < 0.3 ($p < 0.05$) (Table 4).

In terms of treatment responses, the response rate was statistically higher in the group with MLR ≥ 0.30 compared to the group with MLR < 0.30 ($p < 0.05$). In the group with MLR < 0.30 and MLR ≥ 0.30, relapse rate after response did not differ significantly ($p > 0.05$), while the *exitus* rate

Characteristics of the study group (n=80)	Mean ±SD
Age (years)	56.0 ±14.5
Gender	**n (%)**
Female	33 (41.3)
Male	47 (58.5)
Stage	**n (%)**
I	7 (8.8)
II	16 (20)
III	19 (23.8)
IV	38 (47.5)
IPI	**n (%)**
0	9 (11.3)
1	25 (31.3)
2	22 (27.5)
3	21 (26.3)
4	3 (3.8)
Presence of B symptom	**n (%)**
Negative	51 (63.8)
Positive	29 (36.2)
Extranodal involvement	**n (%)**
Negative	40 (50.0)
Positive	40 (50.0)
Bulky Mass	**n (%)**
Negative	58 (72.5)
Positive	22 (27.5)
Immune Phenotype	**n (%)**
Germinal center	22 (27.5)
Non-germinal center	21 (26.3)
Unspecified	37 (46.3)
ECOG	**n (%)**
0-I	64 (80.0)
II-III	16 (20.0)
Transplantation	**n (%)**
Negative	78 (97.5)
Positive	2 (2.5)
Response to Treatment	**n (%)**
No response	2 (2.5)
Partial response	15 (18.8)
Complete response	63 (78.8)
Relapse After Complete Reponse	**n (%)**
Negative	59 (93.7)
Positive	4 (6.3)
Exitus	**n (%)**
Negative	64 (80.0)
Positive	16 (20.0)
Presence of any Comorbidities	**n (%)**
Negative	40 (50.0)
Positive	40 (50.0)
	Mean ±SD
Hemoglobin (gr/dL)	11.8 ±2.4
WBC count (x10^3) (cells/mm^3)	9.1 ±4.8
Neutrophil count (x10^3) (cells/mm^3)	6.5 ±4.6
Monocyte count (x10^3) (cells/mm^3)	0.7 ±0.6
Lymphocyte count (x10^3) (cells/mm^3)	1.6 ±0.8
Platelet count (x10^3) (cells/mm^3)	318.8 ±165.1
NLR	6.1 ±8.6
MLR	0.6 ±0.7
	n (%)
NLR <3.5	44 (55.0)
NLR ≥3.5	36 (45.0)
MLR <0.35	26 (32.5)
MLR ≥0.35	54 (67.5)
Normal LDH (U/L)	50 (62.5)
Abnormal LDH (U/L)	30 (37.5)

IPI: International Prognostic Index, ECOG: Eastern Cooperative Oncology Group, WBC: White blood cell, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, LDH: Lactate dehydrogenase.

Table 1: Demographic and clinical data, immunophenotypes, responses to treatment, last status and laboratory data

was significantly higher in the group with MLR ≥ 0.30 than the group with MLR < 0.30 ($p < 0.05$) (Table 5).

DISCUSSION

Lymphocytes are an important part of innate immunity; they especially play an important role in combating malignant cell population. Similarly, neutrophils are also important in terms of reflecting monocytes in the bloodstream, which have anti-tumor features (15). While neutrophils are an important indicator of inflammatory capacity, lymphocytes reflect the immune response. When past studies are evaluated, different results are encountered. In a study conducted for DLBCL (10), 530 patients with a diagnosis of de novo DLBLC were evaluated in terms of prognosis potency of NLR, but no significant findings were obtained in terms of overall or progression-free survival (PFS). Similarly, in another study conducted with DLBCL patients, 148 patients were examined; PFS and OS were compared with NLR and LMR. We can see that significant statistical findings were obtained in PFS and OS for both ratios (11). In this context, the effect of these rates when considered alone is controversial. When combined with systemic scoring systems, it can be said that they may be important in determining prognosis. In a meta-analysis from 2018 (9), a total of 2515 DLBCL patients in 11 separate studies were examined; NLR was found to be associated with advanced stage disease, advanced age, presence of B symptoms, bone marrow infiltration and high LDH levels. Again, in this study, it was shown that there was a significant relationship between increased NLR and predicted poor OS and PFS.

In the group with NLR ≥ 3.5, neutrophil, monocyte and MLR were significantly higher than the group with NLR < 3.5 ($p < 0.05$). With the same values and NLR in the group with MLR ≥ 0.30, were significantly higher than the group with MLR < 0.3 ($p < 0.05$). This reflected the correlation of NLR and MLR. It was observed that LDH value was significantly higher in the group with MLR ≥ 0.3. This suggests that MLR is more usable to reflect tumor burden.

In the group with NLR ≥ 3.5, the presence of a bulky mass presence was found to be significantly higher. This may be related to the significant increase in inflammatory capacity and the decrease in lymphocytes circulating in the peripheral blood in parallel with the increase in the tumor infiltrating lymphocyte cells (TILc) in the tumor microenvironment, as explained in the literature (16). Both treatment response and *exitus* rates were found to be significantly higher in the same patient group. This was seen as an important outcome for determination of disease survival and response to treatment. Similarly, the presence of bulky mass was significantly higher in the group with MLR ≥ 0.3. This situation is also associated with TILc. In the group with MLR ≥ 0.3; response and *exitus* rates, as in the group with NLR ≥ 3.5, had a statistically significant relationship.

In addition to all these findings, our study had limitations. One of them was the sampling constraints, as the patient population was narrow. Depending on the age of the patients, different NLR and MLR rates may have been obtained due to different absolute lymphocyte and monocyte counts. Similarly, the relationship between the initial WBC and the treatment preferences of the patients were not taken into account. Treatment regimens, preferred with initial bone marrow capacity, caused different results in survival and response rates. Similarly, the regimens' subtypes could not be evaluated separately, due to the fact that they were studied in a limited population.

As a result, in our study, NLR and MLR had a significant correlation. A statistically significant bulky mass presence was demonstrated in the

	Mean ±SD		P value
	NLR<3.5	NLR≥3.5	
Hemoglobin (g/dL)	12.3 ±2.5	11.3 ±2.2	0.059
WBC count (x10³) (cells/mm³)	7.2 ±2.5	11.3 ±5.8	0.000
Neutrophil count (x10³) (cells/mm³)	4.2 ±1.8	9.2 ±5.5	0.000
Monocyte count (x10³) (cells/mm³)	0.61 ±0.33	0.92 ±0.71	0.005
Lymphocyte count (x10³) (cells/mm³)	2.08 ±0.80	1.12 ±0.47	0.000
Platelet count (x10³) (cells/mm³)	285.9 ±125.4	359.0 ±197.9	0.061
NLR	2.1 ±0.8	11.0 ±11.0	0.000
MLR	0.34 ±0.25	1.03 ±0.93	0.000

WBC: White blood cell, MLR: Monocyte-lymphocyte ratio; p<0.05= statistically significant

Table 2: Comparison between neutrophil-lymphocyte ratio (NLR) and laboratory data.

	n (%)		P value
	NLR<3.5	NLR≥3.5	
Response to Treatment			
No response	1 (2.3)	1 (2.8)	0.001
Partial response	3 (6.8)	12 (33.3)	
Complete response	40 (90.9)	23 (6.9)	
Relapse After Complete Response			
Negative	39 (97.5)	20 (87.0)	0.134
Positive	1 (2.5)	3 (13.0)	
Exitus			
Negative	41 (93.2)	23 (63.9)	0.001
Positive	3 (6.8)	13 (36.1)	
MLR <0.35	25 (56.8)	1 (2.77)	0.000
MLR ≥0.35	19 (43.2)	35 (97.3)	
Normal LDH (U/L)	30 (68.1)	20 (55.5)	0.246
Abnormal LDH (U/L)	14 (31.9)	16 (45.5)	

p<0.05= statistically significant

Table 3: Comparison between neutrophil-lymphocyte ratio (NLR) and response-relapse status, exitus, monocyte-lymphocyte ratio (MLR) or lactate dehydrogenase (LDH).

	Mean ±SD		P value
	MLR<0.3	MLR≥0.3	
Hemoglobin (g/dL)	13.4 ±1.8	11.3 ±2.2	0.000
WBC count (x10³) (cells/mm³)	7.8 ±2.5	9.7 ±5.4	0.225
Neutrophil count (x10³) (cells/mm³)	4.6 ±1.8	7.4 ±5.3	0.027
Monocyte count (x10³) (cells/mm³)	0.46 ±0.17	0.89 ±0.62	0.000
Lymphocyte count (x10³) (cells/mm³)	2.40 ±0.79	1.28 ±0.56	0.000
Platelet count (x10³) (cells/mm³)	280.4 ±89.5	337.3 ±189.1	0.363
NLR	2.0 ±0.1	8.1 ±9.9	0.000
MLR	0.20 ±0.06	0.87 ±0.80	0.000

NLR: Neutrophil-lymphocyte ratio, WBC: White blood cell; p<0.05= statistically significant

Table 4: Comparison between neutrophil-lymphocyte ratio (NLR) and laboratory data.

	n (%)		P value
	MLR<0.3	MLR≥0.3	
Response to Treatment			
No response	1 (3.8)	1 (1.9)	0.019
Partial response	0 (0.0)	15 (27.8)	
Complete response	25 (96.2)	38 (70.4)	
Relapse After Complete Response			
Negative	25 (100.0)	34 (89.5)	0.145
Positive	0 (0.0)	4 (10.5)	
Exitus			
Negative	25 (96.2)	39 (72.2)	0.012
Positive	1 (3.8)	15 (27.8)	
Normal LDH (U/L)	22 (84.6)	28 (51.9)	0.005
Abnormal LDH (U/L)	4 (15.4)	26 (48.1)	

p<0.05= statistically significant.

Table 5: Comparison between monocyte-lymphocyte ratio (MLR) and response-relapse status, exitus or lactate dehydrogenase (LDH)

population above the NLR and MLR cut off. In the both groups, treatment responses were significantly lower and *exitus* rates were higher. In addition, LDH was found to be significantly higher in the group with high MLR and was associated with tumor burden. Although not considered sufficient alone for prognosis, these data could be useful in combination with current scoring systems.

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Declaration of Interests

Authors declare no conflicts of interest.

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