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Research Article

Prognostic Value of the Neutrophil-to-Lymphocyte and Lymphocyte-to-Monocyte Ratios and Their Association with the International Prognostic Index in Patients with Diffuse Large B-Cell Lymphoma

Meltem Demirtaş Gülmez[1], Oktay Bilgir[2]

[1]Department of Medical Oncology, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Türkiye
[2]Department of Hematology, Izmir City Hospital, University of Health Sciences, Izmir, Türkiye

Abstract

Objectives: We assessed the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) at diagnosis, their correlations with the International Prognostic Index (IPI), and their impact on survival in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab-based regimens.

Methods: We retrospectively analyzed 139 patients with DLBCL at a single center between 2008 and 2019. Optimal cutoffs were determined by ROC analysis, survival was assessed using the Kaplan–Meier method, and independent predictors were identified using Cox regression analysis.

Results: The optimal cutoffs were 2.90 for NLR and 2.40 for LMR. Both NLR≥2.90 and LMR<2.40 were associated with significantly shorter overall survival (OS) and progression-free survival (PFS) ($p<0.05$). NLR correlated positively with IPI ($r=0.205$, $p=0.021$), whereas LMR correlated negatively ($r=-0.272$, $p=0.001$). In multivariate analysis, ECOG performance status, serum albumin, and NLR independently predicted OS; ECOG performance status, serum albumin, and bone marrow involvement independently predicted PFS. NLR showed the highest discriminatory ability for mortality among NLR, LMR, IPI, and R-IPI.

Conclusion: NLR≥2.90 independently predicts poor OS in DLBCL and may complement existing prognostic indices as an inexpensive marker of host immunity.

Keywords: Diffuse, large B-cell, lymphocytes, lymphoma, monocytes, neutrophils, prognosis; survival analysis

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Lymphomas are a family of malignancies arising from cells of the immune system. Among these, non-Hodgkin lymphomas (NHLs) constitute a biologically diverse category. They are among the leading hematological cancers worldwide. Within this group, diffuse large B-cell lymphoma (DLBCL) is the dominant type, accounting for approximately one-quarter to one-third of NHL diagnoses in industrialized regions.[1] The 1-year survival rate without treatment is approximately 50%. However, modern treatment regimens make the disease curable in a significant proportion of cases.

Address for correspondence: Meltem Demirtaş Gülmez, MD, Department of Medical Oncology, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Türkiye
Phone: +90 535 796 22 09 **E-mail:** drmeltemgulmez@gmail.com

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Since its introduction in 1993, the International Prognostic Index (IPI) has served as the principal risk-assessment tool in DLBCL and is based on five clinical parameters: patient age, disease stage according to the Ann Arbor classification, serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and the number of extranodal involvement sites.[2] The advent of the anti-CD20 monoclonal antibody rituximab substantially altered survival expectations in CD20-expressing lymphomas and called into question the prognostic separation provided by the original index.[3] To address this, a Revised IPI (R-IPI) was developed and demonstrated better risk discrimination among individuals receiving rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[4]

Although improved, IPI-based systems are limited to clinical and tumor-related variables and overlook the contributions of immune competence and the surrounding tumor milieu—two elements increasingly appreciated as key factors in lymphoma pathobiology.[5] Inflammatory infiltrates within neoplastic tissue exert dual effects, fostering or restraining malignant growth depending on their composition.[6,7] Lymphocyte populations contribute to antineoplastic surveillance via cytotoxic mechanisms,[8] whereas macrophages derived from peripheral monocytes may shift toward a tumor-promoting phenotype that supports disease progression and helps the tumor evade immune control.[9] In addition, high neutrophil counts and persistent inflammation can further sustain malignancy through the release of protumorigenic cytokines.[10]

NLR and LMR, calculated directly from standard complete blood counts, collectively summarize systemic inflammatory activity and adaptive immune capacity. Unfavorable values of these indices have been associated with poor outcomes in various solid malignancies.[11–13] Data suggest a similar prognostic effect in DLBCL.[14,15] However, reported findings remain inconsistent. Questions persist regarding the most informative thresholds and the additional value these markers may provide compared with IPI or R-IPI, particularly when examined in single-institution cohorts receiving rituximab-containing treatment.

Our study aimed to investigate the prognostic significance of pretreatment NLR and LMR values. Other objectives of our study included examining their associations with IPI and R-IPI, evaluating their relationships with the initial therapeutic response, and exploring their independent contributions to OS and PFS in a DLBCL population managed with rituximab-containing chemotherapy.

Methods

Study Design And Patients

Adults aged 18 years and older who were diagnosed with biopsy-confirmed DLBCL at the Hematology Clinic of XXX Hospital between January 2008 and May 2019 were included in the study. Records were reviewed retrospectively. Individuals with an ongoing infection, known HIV positivity, liver cirrhosis or advanced liver disease, a history of another malignancy, or prior exposure to anti-inflammatory, immunosuppressive, or monoclonal antibody agents administered for indications unrelated to the index lymphoma were excluded from the study. A final sample of 139 patients was obtained after applying these criteria. Ethical approval was obtained from the University of Health Sciences, İzmir Bozyaka Training and Research Hospital Institutional Ethics Committee (approval no. 05, dated May 22, 2019), and all procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Data Collection and Definitions

Basic demographic information, clinical characteristics, laboratory test results, chemotherapy regimens, response assessments, and follow-up outcomes were obtained from the hospital records. These included age, sex, frequency of B symptoms, ECOG score, hemoglobin level, absolute neutrophil, lymphocyte, and monocyte counts, platelet count, LDH, C-reactive protein (CRP), and albumin concentration. All calculations were performed using the hospital laboratory's limits of normality. NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. LMR was calculated as the ratio of lymphocytes to monocytes.

Staging followed the revised Ann Arbor system, as updated by the Lugano consensus, with whole-body 18F-FDG PET/CT used as the principal modality and contrast-enhanced cervical, thoracic, and abdominal CT serving as an alternative when PET/CT could not be performed.[16] Marrow infiltration was evaluated by single-sided iliac crest biopsy, PET/CT imaging, or a combination of both. Immunohistochemical classification into germinal-center versus non-germinal-center subtypes using the Hans algorithm was feasible in 62 cases.[17] IPI and R-IPI risk scores were derived for every patient following the original methodology.[2,4]

Treatment and Response Evaluation

Each patient was treated with a protocol that included rituximab. Initial treatment consisted of three R-CHOP cycles (n=15), six to eight R-CHOP cycles (n=82), six R-CHOP cycles followed by eight rituximab maintenance doses (n=10),

R-CVP (n=3), or the attenuated R-mini-CHOP variant (n=4), in conjunction with involved-field radiotherapy. Twenty-five patients initiated rituximab-based treatment. However, they were unable to complete the planned course of treatment because of adverse effects or early death. Therapeutic response was assessed by PET/CT or contrast-enhanced CT and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the revised Lugano framework.[16] Those showing primary refractoriness or relapse who were eligible for autologous hematopoietic stem cell transplantation were referred to a specialized transplant unit.

Overall survival (OS) was measured as the time from diagnosis to death from lymphoma or its treatment or to the date of the last clinical contact. Disease-free survival (PFS) was calculated as the time from diagnosis to objectively documented progression, relapse after complete remission, or lymphoma-related death. Eleven patients whose causes of death were unrelated to lymphoma were excluded from the survival models. This left 128 patients for time-to-event calculations. Vital status information was cross-validated using the national death registry.

Statistical Analysis

All computations were carried out using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). Numerical variables were summarized either as the mean with standard deviation or as the median with range, depending on distributional characteristics determined by the Kolmogorov–Smirnov and Shapiro–Wilk tests; categorical data were reported as counts with percentages. Between-group testing employed Student's t-test or the Mann–Whitney U test for numerical data, whereas categorical comparisons relied on the chi-square test. Survival estimates were generated using Kaplan–Meier curves and compared using the log-rank test. The most informative NLR and LMR cut-off points for predicting all-cause mortality were obtained from ROC analysis by maximizing the Youden index (J=-sensitivity+specificity−1). Spearman's coefficient was used to assess correlations between the two ratios and the IPI score. Covariates reaching statistical significance in univariate Cox analysis were carried forward into multivariable Cox proportional hazards models using the enter method to identify independent predictors of OS and PFS. Statistical significance was defined as a two-tailed $p<0.05$.

Results

Patient Characteristics

The mean age of the analysis cohort was 59.1±14 years. The mean follow-up period was 30.5 months (range, 1–138 months). Of the 139 individuals observed, 76 were male and 63 were female. More than half (53.2%) were over 60 years of age. B symptoms were reported by 42.4%, and 51.1% had an ECOG score of 2 or higher. Advanced-stage disease (Ann Arbor III–IV) was present in 64% of cases, and 64% had involvement of at least one extranodal region. Bone marrow infiltration was documented in 13.6%. Of the 62 patients with evaluable immunohistochemistry, 82.3% were classified in the non-germinal center category according to the Hans algorithm. According to the IPI, the risk distribution was 28.1% low risk, 20.9% low-to-moderate risk, 30.2% high-to-moderate risk, and 20.9% high risk. Detailed baseline data are presented in Table 1.

Treatment Response and Survival

Of the 139 patients, 100 (71.9%) successfully completed the planned first-line treatment regimen. Of the remaining

Table 1. Demographic profile, clinical features, and laboratory findings at baseline among the 139 study patients with diffuse large B-cell lymphoma

Characteristic	n	%
Age, years - mean ± SD	59.1±14	
Age, years - median (range)	61 (18-85)	
> 60 years	74	53.2
Sex - male	76	54.7
B symptoms present	59	42.4
ECOG performance status 2-4	71	51.1
Ann Arbor stage III-IV	89	64.0
Extranodal involvement ≥ 1 site	89	64.0
≥ 2 extranodal sites	36	25.9
Bone marrow involvement	19	13.6
Elevated LDH	69	49.6
Elevated CRP (> 5 mg/L)	96	69.1
Albumin < 3.5 g/dL	25	18.0
Non-germinal center subtype (Hans, n=62)	51	82.3
IPI - low risk (0-1)	39	28.1
IPI - low-intermediate (2)	29	20.9
IPI - high-intermediate (3)	42	30.2
IPI - high (4-5)	29	20.9
R-IPI - very good (0)	11	7.9
R-IPI - good (1-2)	57	41.0
R-IPI - poor (3-5)	71	51.1

CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; R-IPIÇ: Revised International Prognostic Index; SD: Standard deviation.

patients, 25 (18%) died during treatment or before response assessment. The others either did not initiate treatment or refused treatment. Response outcomes were distributed as follows: 55.4% complete response (CR), 3.6% partial response (PR), 0.7% stable disease (SD), and 12.2% progressive disease (PD). After excluding 11 cases of death due to non-lymphoma causes, 128 patients were included in the survival analyses. Five-year overall survival (OS) reached 58.2%, and 3-year disease-free survival (PFS) reached 52%; the median OS was 83.1 months (95% CI, 87–118), and the median PFS was 69.4 months (95% CI, 63.1–90.6).

In univariate analyses, the presence of B symptoms, an ECOG score of 2–4, involvement of multiple extranodal sites, bone marrow infiltration, and a serum albumin level below 3.5 g/dL were associated with shorter overall survival (OS) and/or disease-free survival (PFS), whereas age, sex, hemoglobin, LDH, CRP, and Hans-defined cell of origin were not associated with these outcomes. Risk stratification according to the IPI or R-IPI yielded statistically significant stratification for both endpoints ($p \leq 0.007$). Five-year OS rates for the four IPI strata (low, low-to-moderate, high-to-moderate, and high) were 76.4%, 61.8%, 57.9%, and 30.3%, respectively. When the shortened treatment regimen (three R-CHOP cycles plus radiotherapy) was compared with the standard six- to eight-cycle R-CHOP approach, no significant difference was found in overall survival (OS) or disease-free survival (PFS) ($p=0.786$ and $p=0.427$, respectively). Initial treatment response was strongly associated with overall survival. Three-year overall survival was 89.3% after complete response (CR), 80% after partial response (PR), and only 13.3% after progressive disease (PD) ($p<0.001$).

NLR Cutoff, Correlations, and Survival

Through ROC analysis, an NLR threshold of 2.90 emerged as the optimal value for discriminating mortality, providing 86% sensitivity, 50% specificity, an AUC of 0.674, and $p=0.001$ (Fig. 1). The proportion of patients exceeding this cutoff was 89 of 139 (64%). The ratio showed a direct correlation with the IPI score ($r=0.205$, $p=0.021$), as well as with a poorer initial response ($r=0.263$, $p=0.004$). Compared with their counterparts, individuals with NLR≥2.90 had higher proportions of ECOG≥2, elevated LDH and CRP levels, low albumin levels, and higher IPI/R-IPI categories (all $p<0.05$); the two NLR groups were similar in terms of age, sex, B symptoms, extranodal involvement, marrow status, stage, and Hans subtype (Table 2).

Five-year OS reached 81% when NLR remained below 2.90 but fell to 45.8% above that threshold (median OS, 116.2 vs. 65.7 months; $p<0.001$). Likewise, 3-year PFS was 66.2% versus 44.7% across the two strata (median PFS, 92.8 vs. 57.7 months; $p=0.006$) (Fig. 2).

LMR Cutoff, Correlations, and Survival

For LMR, the optimal cutoff point obtained by ROC analysis was 2.40, with a sensitivity of 69%, specificity of 56%, AUC of 0.630, and $p=0.032$. Fifty-one of 128 patients (42.1%) fell below this value. The ratio showed an inverse relationship with the IPI score ($r=-0.272$, $p=0.001$) and a positive correlation with the response category ($r=0.210$, $p=0.048$). Values below the 2.40 threshold were significantly associated with ECOG≥2, two or more extranodal sites, high LDH levels, hypoalbuminemia, and high-risk IPI/R-IPI categories (Table 3).

The 5-year overall survival rate was 45% in patients with an LMR value below 2.40 and 67.3% in those with a value greater than or equal to 2.40 (median overall survival, 66.7 months vs. 94.9 months; $p=0.019$). The 3-year progression-free survival rate was similarly 38.6% versus 61.2% (median progression-free survival, 53.6 months vs. 66.4 months; $p=0.022$) (Fig. 3).

Multivariate Analysis and Comparison of Prognostic Markers

Univariate Cox modeling identified ECOG score, number of extranodal regions, serum albumin, IPI, R-IPI, NLR, and LMR as factors significantly associated with OS. For PFS, the corresponding factors were B symptoms, ECOG score, bone marrow infiltration, albumin, IPI, R-IPI, NLR, and LMR (Table 4). In the multivariate model for OS, three variables retained their independent prognostic significance. These variables were ECOG performance status (HR, 4.17; 95% CI, 2.04–

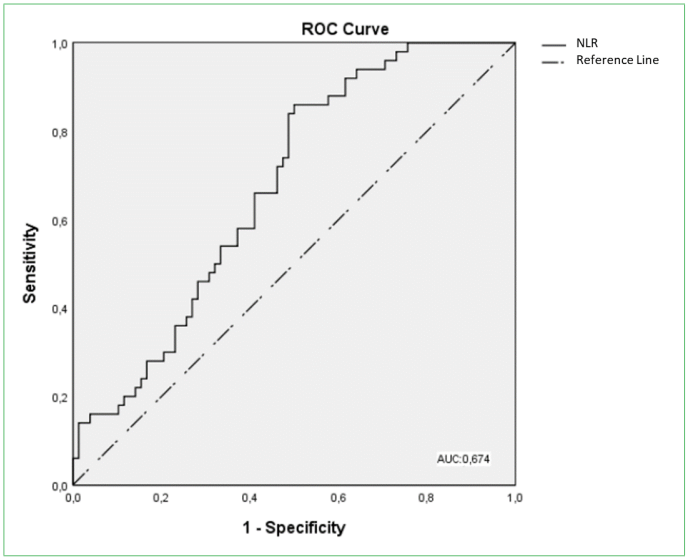

Figure 1. ROC curves illustrating the discriminative thresholds for NLR (AUC 0.674) and LMR (AUC 0.630) in predicting all-cause mortality among patients with diffuse large B-cell lymphoma.

Table 2. Distribution of patient features stratified by neutrophil-to-lymphocyte ratio (NLR) category (threshold 2.90)

Characteristic	NLR < 2.90 (n=50) n (%)	NLR ≥ 2.90 (n=89) n (%)	OR (95% CI)	p
Age > 60 years	24 (52.2)	42 (51.2)	0.96 (0.47-1.98)	0.917
Male sex	25 (54.3)	44 (53.7)	1.97 (0.47-2.01)	0.940
B symptoms	18 (39.1)	39 (47.6)	1.41 (0.68-2.94)	0.357
ECOG 2-4	15 (32.6)	49 (59.8)	3.07 (1.44-6.55)	0.003
≥ 2 extranodal sites	7 (15.2)	24 (29.3)	2.31 (0.91-5.87)	0.075
Bone marrow involvement	5 (10.9)	14 (17.1)	1.69 (0.57-5.03)	0.344
Advanced stage (III-IV)	27 (58.7)	56 (68.3)	1.52 (0.72-3.21)	0.275
Elevated LDH	16 (34.8)	47 (57.3)	2.52 (1.19-5.32)	0.014
Elevated CRP	26 (56.5)	61 (74.4)	2.23 (1.04-4.80)	0.038
Albumin < 3.5 g/dL	2 (4.3)	19 (23.2)	6.64 (1.47-29.95)	0.006
IPI high-intermediate/high	17 (37.0)	49 (59.8)	2.53 (1.20-5.33)	0.013
R-IPI poor	17 (37.0)	49 (59.8)	2.53 (1.20-5.33)	0.013

CI: Confidence interval; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OR: Odds ratio; R-IPI: Revised International Prognostic Index.

8.54; p<0.001), serum albumin (HR, 2.19; 95% CI, 1.07–4.49; p=0.032), and NLR≥2.90 (HR, 3.00; 95% CI, 1.26–7.14; p=0.013). Independent predictors of PFS were ECOG performance status (HR, 6.03; 95% CI, 3.02–12.04; p<0.001), albumin (HR, 2.33; 95% CI, 1.16–4.66; p=0.017), and bone marrow involvement (HR, 3.59; 95% CI, 1.48–8.72; p=0.005). NLR and LMR did not retain their independent significance in this model.

Direct ROC comparison of the four prognostic markers for mortality discrimination produced AUC values of 0.680 for NLR, 0.616 for LMR, 0.664 for IPI, and 0.634 for R-IPI; therefore, NLR offered the greatest discriminatory capacity among the tested indices (Fig. 4).

Discussion

In a single-center retrospective DLBCL series of 139 patients managed with rituximab-based protocols, baseline NLR and LMR values were associated with overall survival (OS) and disease-free survival (PFS), followed IPI risk categories, and reflected the quality of response to first-line treatment. After accounting for classical prognostic variables, NLR≥2.90 emerged as an independent predictor of OS, along with poor ECOG performance status and hypoalbuminemia, whereas LMR failed to maintain its independence in the adjusted model. Specifically, direct comparison among the four indices revealed that NLR had greater discriminatory power for mortality than IPI, R-IPI, or LMR.

There is increasing evidence that systemic inflammation, immune capacity, and the microenvironment surrounding malignant cells collectively influence lymphoma behavior. Considering all these effects, these ratios can be observed to have a biological basis for their prognostic importance. Neutrophils contribute to an environment that promotes

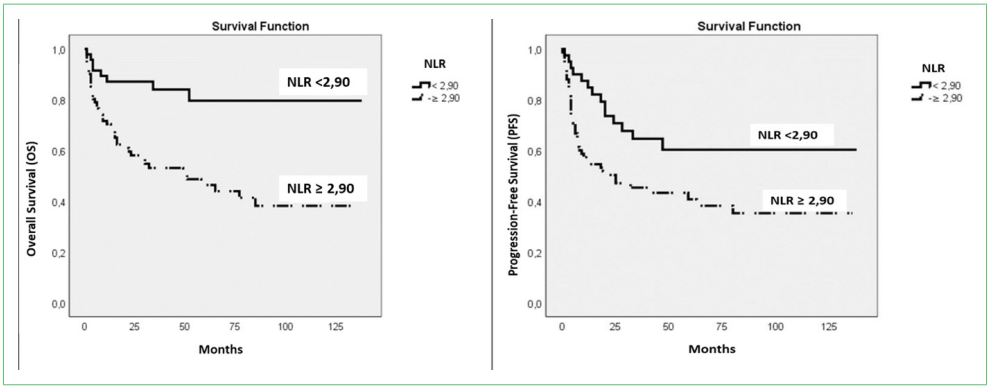

Figure 2. Kaplan-Meier estimates for overall survival (panel A) and progression-free survival (panel B), stratified by an NLR threshold of 2.90.

Table 3. Distribution of patient features stratified by lymphocyte-to-monocyte ratio (LMR) category (threshold 2.40).

Characteristic	LMR < 2.40 (n=51) n (%)	LMR ≥ 2.40 (n=77) n (%)	OR (95% CI)	p
Age > 60 years	27 (52.9)	39 (50.6)	1.10 (0.54-2.23)	0.799
Male sex	29 (56.9)	40 (51.9)	1.22 (0.60-2.49)	0.385
B symptoms	28 (54.9)	29 (37.7)	2.02 (0.98-4.14)	0.055
ECOG 2-4	32 (62.7)	32 (41.6)	2.37 (1.15-4.90)	0.019
≥ 2 extranodal sites	17 (33.3)	14 (18.2)	2.25 (1.00-5.12)	0.049
Bone marrow involvement	8 (15.7)	11 (14.3)	1.12 (0.41-3.00)	0.827
Advanced stage (III-IV)	37 (72.5)	46 (59.7)	1.78 (0.83-3.83)	0.137
Elevated LDH	33 (64.7)	30 (39.0)	2.87 (1.38-5.99)	0.004
Elevated CRP	37 (72.5)	50 (64.9)	1.43 (0.66-3.09)	0.366
Albumin < 3.5 g/dL	17 (33.3)	4 (5.2)	9.13 (2.85-29.19)	<0.001
IPI high-intermediate/high	34 (66.7)	32 (41.6)	2.81 (1.35-5.88)	0.005
R-IPI poor	34 (66.7)	32 (41.6)	2.81 (1.35-5.88)	0.005

CI: Confidence interval; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OR: Odds ratio; R-IPI: Revised International Prognostic Index.

tumor formation through the release of mediators, including IL-10, TNF-α, and vascular endothelial growth factor.[10] Lymphocytes directly drive antitumor cytotoxic activity.[8] Circulating monocytes, after recruitment, can transform into tumor-associated macrophages, which reduce antitumor responses and aid neoplastic progression.[9] In this context, an increased NLR together with a decreased LMR reasonably reflects an imbalance that promotes inflammation rather than effective adaptive immunity, thereby supporting tumor formation.

Our cohort's NLR threshold of 2.90 falls within the spectrum reported in previous DLBCL studies. Although a Mayo Clinic group led by Porrata established a cutoff point of 3.5, analyses by Wang and Spassov determined values of 2.81 and 3.01, respectively, both validating NLR as an independent predictor of OS.[14,18,19] Higher thresholds, ranging from 4.35 to 5.54, have been identified elsewhere. In these studies, NLR retained significance only at the univariate level. Such differences may reflect variations in cohort composition, treatment exposure, and the definitions used for survival endpoints.[20,21] This methodological variability explains the differing multivariate outcomes reported in the literature. It also underscores the need for prospective validation using uniform threshold criteria.

The LMR threshold of 2.40 that we observed is comparable to the value of 2.60 reported by Rambaldi and colleagues, whose work positioned LMR as an independent determinant of both OS and PFS in patients with DLBCL receiving

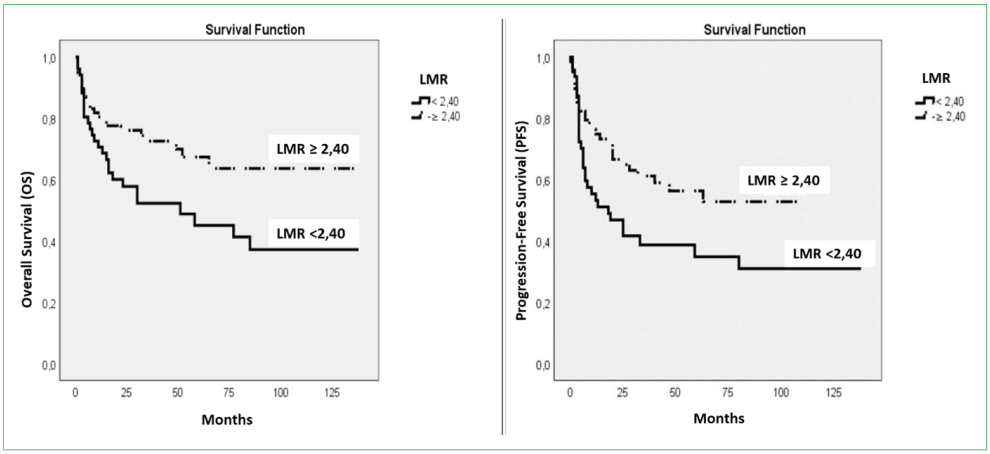

Figure 3. Kaplan-Meier estimates for overall survival (panel A) and progression-free survival (panel B), stratified by an LMR threshold of 2.40.

Table 4. Cox proportional hazards modeling, univariate and multivariable results for factors related to overall survival (OS) and progression-free survival (PFS)

	Univariate OS HR (95% CI), p	Multivariate OS HR (95% CI), p	Univariate PFS HR (95% CI), p	Multivariate PFS HR (95% CI), p
B symptoms	1.69 (0.97-2.96), 0.065	-	2.02 (1.20-3.41), 0.009	1.40 (0.81-2.41), 0.229
ECOG 2-4	4.96 (2.53-9.71), <0.001	4.17 (2.04-8.54), <0.001	5.98 (3.21-11.15), <0.001	6.03 (3.02-12.04), <0.001
≥ 2 extranodal sites	1.90 (1.05-3.43), 0.033	1.44 (0.69-3.00), 0.327	1.38 (0.77-2.46), 0.281	0.64 (0.30-1.37), 0.248
Bone marrow involvement	1.61 (0.78-3.34), 0.199	-	2.07 (1.06-4.04), 0.032	3.59 (1.48-8.72), 0.005
Albumin < 3.5 g/dL	2.81 (1.51-5.22), 0.001	2.19 (1.07-4.49), 0.032	2.66 (1.48-4.77), 0.001	2.33 (1.16-4.66), 0.017
IPI high-int./high	2.32 (1.29-4.18), 0.005	-	2.27 (1.32-3.89), 0.003	-
NLR ≥2.90	4.18 (1.88-9.30), <0.001	3.00 (1.26-7.14), 0.013	2.29 (1.23-4.26), 0.009	1.04 (0.51-2.13), 0.911
LMR <2.40	1.92 (1.10-3.35), 0.022	0.73 (0.36-1.49), 0.391	1.80 (1.07-3.02), 0.026	0.89 (0.46-1.71), 0.727

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IPI: International Prognostic Index; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio. Covariates without univariate significance were not carried forward to multivariable modeling (denoted). The adjusted multivariable models incorporated ECOG score, ≥ 2 extranodal sites, albumin level, B symptoms, marrow involvement, NLR, and LMR.

rituximab-based regimens.[22] In our cohort, LMR was significantly associated with OS and PFS in univariate testing but lost its independent role after multivariable adjustment, suggesting that LMR is heavily influenced by tumor burden and other coexisting prognostic factors. Consistent with this observation, Ji and coworkers demonstrated that an LMR/LDH composite outperformed LMR alone in multivariable settings, supporting the rationale that combined indices integrating immunity and tumor burden may provide superior prognostic resolution.[23]

This study offers several distinctive features beyond reinforcing previous observations. First, rituximab-based treatment was uniformly administered at a single institution. This minimized variability in clinical management. Second, non-lymphoma-related deaths were excluded from the survival analyses. This made the prediction of disease-specific outcomes more sensitive. Third, a simultaneous direct ROC comparison of NLR, LMR, IPI, and R-IPI was performed in the cohort. It objectively ranked NLR as having the highest discriminatory power. These findings are consistent with previous suggestions that integrating immune-related parameters into established clinical scores can improve risk stratification in the modern rituximab-treated population.[2,4]

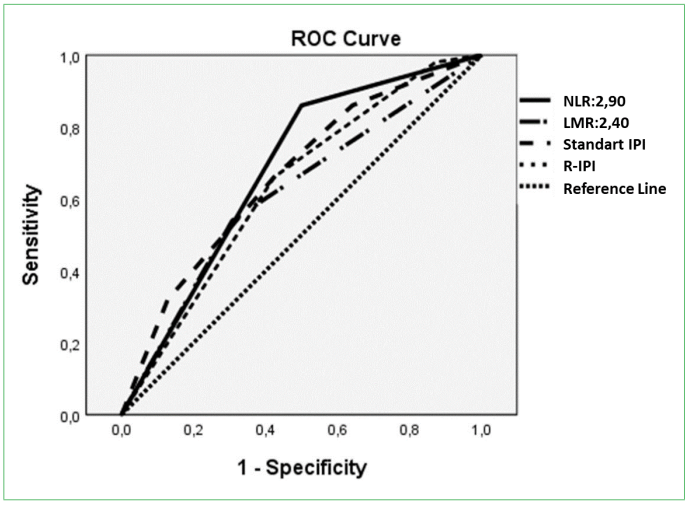

Figure 4. Head-to-head ROC comparison of NLR, LMR, IPI, and R-IPI for predicting all-cause mortality.

The findings further validate the prognostic weight of traditional clinical variables. A poor ECOG score, advanced IPI-defined disease, involvement of multiple extranodal regions, bone marrow infiltration, and low serum albumin levels were all associated with worse outcomes. Hypoproteinemia, an integral reflection of both nutritional reserve and chronic inflammatory burden, remained independently associated with both OS and PFS, mirroring observations from previously published series.[24] Notably, Hans-based immunohistochemical classification (germinal center origin and non-germinal center origin) was not associated with survival in our cohort. The limited number of cases for which immunohistochemical data were available (n=62) and reliance on the Hans surrogate, instead of gene expression profiling, which remains the reference standard but is rarely accessible in daily practice, may be the underlying reasons for this unfavorable finding.[17]

Some limitations should be considered. Because the analysis was retrospective and limited to a single center, generalizability is naturally restricted. Comprehensive cell-of-origin assessment for the entire cohort and FISH-based detection of double- or triple-hit rearrangements were not available, which prevented specific subgroup analyses. Bone marrow sampling was largely unilateral, increasing the possibility of underestimating bone marrow involvement. In addition,

NLR and LMR show demographic variability in healthy populations, reinforcing the need for population-specific normative ranges.[25] Finally, the discriminatory performance of both ratios in predicting individual mortality was only moderate (AUC range, 0.61–0.68). This suggests that they are best viewed as complementary to, rather than replacements for, established prognostic tools.

Despite these constraints, NLR and LMR remain inexpensive and widely accessible parameters that provide prognostic information at essentially no incremental laboratory expense. Embedding them within the IPI/R-IPI framework in larger multicenter prospective studies, potentially together with tumor-burden surrogates such as LDH or β2-microglobulin, could refine existing risk-prediction models and help identify patients who might benefit from intensified treatment strategies or earlier enrollment in clinical investigations.

Conclusion

In a DLBCL population managed with rituximab-inclusive protocols, baseline NLR≥2.90 and LMR<2.40 were both associated with higher IPI risk, a poorer first-line response, and shorter overall survival (OS) and disease-free survival (PFS). NLR emerged as an independent predictor of OS, along with ECOG performance status and serum albumin, and demonstrated the strongest discriminatory capacity for mortality among the indices examined. Because both ratios are readily obtainable from routine laboratory data, they can be easily integrated into daily risk assessment in conjunction with IPI-based scoring; however, prospective multicenter studies are needed to validate these results.

Disclosures

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences, İzmir Bozyaka Training and Research Hospital Institutional Ethics Committee (approval no. 05, dated May 22, 2019), and all procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Individual patient consent was waived by the Ethics Committee due to the retrospective nature of the study.

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