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Article *in* Clinical Lymphoma, Myeloma and Leukemia · May 2020

DOI: 10.1016/j.clml.2020.04.016

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Original Study

A Multi-Institutional Validation of the Prognostic Value of the Neutrophil-to-Lymphocyte Ratio in Patients With Diffuse Large B-Cell Lymphoma: A Study From The Latin American Group of Lymphoproliferative Disorders (GELL)

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Abstract

We aimed at investigating the prognostic role of the neutrophil-to-lymphocyte ratio (NLR) in 2 independent cohorts of Latin American patients with diffuse large B-cell lymphoma treated with chemoimmunotherapy. An optimal NLR cutoff ≥ 4 was determined using receiver operating characteristic analysis. In multivariate models, NLR ≥ 4 was independently associated with lower odds for complete response and worse survival in the learning and the validation cohort. The adverse prognostic value of NLR ≥ 4 was independent of the

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Submitted: Mar 19, 2020; Revised: Apr 25, 2020; Accepted: Apr 25, 2020

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2152-2650/$ - see frontmatter
https://doi.org/10.1016/j.clml.2020.04.016

International Prognostic Index and the National Comprehensive Cancer Network-International Prognostic Index score.

Introduction: We aimed at investigating the prognostic role of the neutrophil-to-lymphocyte ratio (NLR) in 2 independent cohorts of Latin American patients with diffuse large B-cell lymphoma (DLBCL) treated with chemoimmunotherapy. **Patients and Methods:** The learning cohort was composed of 274 patients and the validation cohort of 323 patients, for a total of 597 patients. An optimal NLR cutoff ≥ 4 was determined using receiver operating characteristic analysis. **Results:** In multivariate models, NLR ≥ 4 was independently associated with lower odds for complete response to chemoimmunotherapy in the learning (odds ratio, 0.46; $P = .006$) and the validation cohort (odds ratio, 0.49; $P = .01$), and independently associated with worse survival in the learning (hazard ratio, 1.55; $P = .04$) and the validation cohort (hazard ratio, 1.80; $P = .003$). **Conclusions:** The adverse prognostic value of NLR ≥ 4 was independent of the International Prognostic Index and the National Comprehensive Cancer Network-International Prognostic Index score. Based on the results of this multi-institutional study, NLR ≥ 4 emerges as an adverse prognostic factor in Latin American patients with DLBCL treated with chemoimmunotherapy.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Biomarkers, DLBCL, NLR, Overall survival, Prognostic factor

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) subtype, accounting for about 30% to 40% of the cases of lymphoma in the United States and Europe.[1] In Latin America, DLBCL is also the most common subtype of NHL, reported at a frequency of up to 50% of the cases.[2] A proportion of patients with DLBCL can be cured with standard chemoimmunotherapy regimens. However, the prognosis of patients with DLBCL remains heterogeneous, and better prognostic tools are required to improve our prognostic estimates.[3]

The International Prognostic Index (IPI) and the National Comprehensive Cancer Network (NCCN)-IPI are arguably the most commonly used prognostic models for DLBCL in the era of chemoimmunotherapy.[4,5] The neutrophil-to-lymphocyte ratio (NLR) is as an adverse prognostic factor in different types of solid tumors such as breast, lung, hepatocellular, pancreatic, gastric, and lung cancers.[6-11] In hematologic neoplasms, several studies have suggested a prognostic role for the NLR in patients with classical Hodgkin lymphoma, multiple myeloma, and T-cell lymphoma.[12-16] Inflammation has been reported to be a hallmark of tumorigenesis and is associated with neutrophilia, whereas lymphopenia has been associated with systemic immunodeficient processes.[17-19] The relation between neutrophilia and lymphopenia, in the context of inflammation, seems to be associated with specific molecular and cytokine profiles.[20-24] In this context, the NLR might be a biomarker of underlying inflammatory and immunodeficient processes in patients with cancer.

The main objective of the present study was to establish the association between the NLR, response rates, and survival outcomes in patients with DLBCL treated with chemoimmunotherapy in 2 independent cohorts, learning and validation cohorts, of Latin American patients.

Patients and Methods

Patient Selection

The present study had an observational, transversal, analytical, and retrospective design. The study population was composed of consecutive patients with DLBCL, newly diagnosed and treated at participating institutions between 2010 and 2012. Inclusion criteria included histopathologic diagnosis of DLBCL, patients older than 18 years, clinical history with complete clinical information and follow-up, and having received treatment at participating institutions. Exclusion criteria included histologic transformation, primary mediastinal DLBCL, central nervous system involvement, and active infection with hepatitis B, hepatitis C, or HIV. Patients were treated with standard chemoimmunotherapy (R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone]), which was administered every 3 weeks with a curative intent. No patient was treated in the context of a clinical trial. The learning cohort was composed of patients treated in centers from Argentina, Chile, Colombia, Peru, and Venezuela. The validation cohort was composed of patients treated in centers from Mexico (GELMEX; Grupo de Estudio para el Linfoma Mexicano). All together, we legally constitute the Latin American Group of Lymphoproliferative Disorders (GELL). This study was approved by each local Institutional Review Board.

Data Gathering

Relevant clinical and pathologic data were gathered, which included but were not limited to age, gender, performance status, clinical stage, extranodal sites of involvement, serum lactate dehydrogenase (LDH) level, presence of B symptoms, response to therapy, and overall survival (OS). The IPI and NCCN-IPI were estimated based on prior publications. For purpose of this study, absolute neutrophil and lymphocyte counts were collected between the time of DLBCL diagnosis and treatment initiation. The NLR was estimated by dividing the absolute neutrophil count (ANC) over the absolute lymphocyte count (ALC). Response to therapy was assessed using standard criteria, whenever possible.[29] OS was defined as the time between diagnosis and last follow-up or death from any cause.

Statistical Analysis

Clinicopathologic data are presented using descriptive statistics, and categorical characteristics between groups compared using the

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Table 1 Patients' Characteristics From Learning and Validation Cohorts

	Learning Cohort (n = 274), n (%)	Validation Cohort (n = 323), n (%)	*P* Value
Age ≥ 60 y	164 (60)	137 (42)	<.001
ECOG ≥ 1	82 (30)	78 (24)	.11
Elevated LDH level	194 (72)	155 (48)	<.001
≥1 extranodal site	34 (12)	56 (17)	.10
Stage III or IV	131 (48)	200 (62)	.001
IPI score			
Low risk	72 (27)	125 (39)	.03
Low-intermediate risk	84 (31)	85 (26)	
High-intermediate risk	77 (28)	80 (25)	
High risk	34 (13)	33 (10)	
NCCN-IPI score			
Low risk	31 (11)	43 (13)	.03
Low-intermediate risk	93 (32)	135 (42)	
High-intermediate risk	133 (46)	121 (37)	
High risk	30 (10)	24 (7)	
Response to R-CHOP			
Complete response	209 (72)	209 (74)	.67
Partial response	39 (13)	31 (11)	
No response	44 (15)	41 (15)	
NLR ≥ 4	123 (42)	132 (41)	.84

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Score; LDH = lactate dehydrogenase; NCCN = National Comprehensive Cancer Network; NLR = neutrophil-to-lymphocyte ratio; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

χ^2 test. The optimal NLR cutoff level was selected by performing receiver operating characteristic (ROC) analysis using outcome as the binary reference variable (ie, dead or alive) versus NLR as a continuous reference variable.[25] Univariate and multivariate logistic regression models were fitted to evaluate the association of clinical variables and complete response (CR) to therapy. The outcome of interest of the logistic regression analysis is reported as odds ratio (OR) with 95% confidence interval (CI). For the survival analysis, the Kaplan-Meier method was used to generate OS curves, which were compared using the log-rank test. The Cox proportional hazard regression method was used to fit univariate and multivariate survival models for OS. The outcome of interest of the survival

Table 2 Univariate and Multivariate Logistic Regression Analysis for Complete Response in Learning and Validation Cohorts

	Univariate Analysis		Multivariate Analysis	
Learning Cohort	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age ≥ 60 y	1.47 (0.88-2.45)	.14	1.55 (0.89-2.70)	.12
ECOG ≥ 1	0.59 (0.35-1.02)	.06	0.67 (0.37-1.20)	.18
Elevated LDH level	0.56 (0.31-1.03)	.06	0.68 (0.36-1.28)	.23
≥ 1 extranodal site	0.41 (0.20-0.84)	.01	0.66 (0.29-1.48)	.31
Stage III or IV	0.38 (0.20-0.60)	<.001	0.39 (0.21-0.70)	.002
NLR ≥ 4	0.46 (0.27-1.63)	.003	0.46 (0.26-0.80)	.006
	Univariate Analysis		**Multivariate Analysis**	
Validation Cohort	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age ≥ 60 y	0.75 (0.44-1.29)	.30	0.66 (0.37-1.17)	.16
ECOG ≥ 1	0.60 (0.32-1.11)	.10	0.78 (0.40-1.52)	.47
Elevated LDH level	0.38 (0.22-0.66)	.001	0.53 (0.29-0.97)	.04
≥1 extranodal site	0.39 (0.20-0.77)	.007	0.55 (0.26-1.18)	.12
Stage III or IV	0.50 (0.28-0.90)	.02	0.70 (0.37-1.34)	.29
NLR ≥ 4	0.41 (0.23-0.70)	.001	0.49 (0.27-0.88)	.01

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio.

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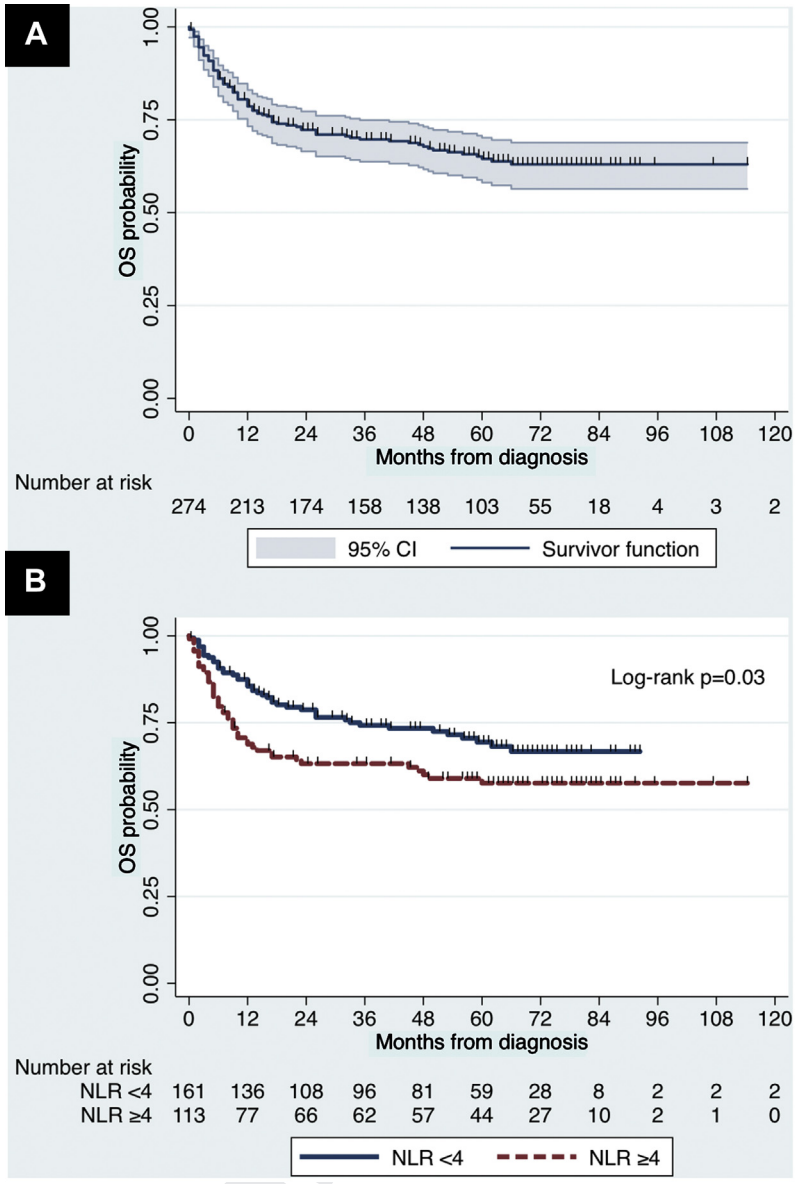
Figure 1 Kaplan-Meier Curves for Overall Survival for the Entire Cohort (A) and by Neutrophil-To-Lymphocyte Ratio (Learning Cohort) (B)



Abbreviations: CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival.

analysis was reported as the hazard ratio (HR) with 95% CI of death from any cause. *P*-values < .05 were considered statistically significant. Calculations and graphs were obtained using STATA version 15 (StataCorp, College Station, TX).

Results

Patients' Characteristics

A total of 597 patients were included in this study. The learning and validation cohorts were composed of 274 and 323 patients, respectively. The patients' characteristics from the learning and validation cohorts are shown in Table 1. There was a higher proportion of patients with age ≥ 60 years and elevated serum LDH level in the learning cohort, and a higher proportion of patients with stage III or IV in the validation cohort. There were no differences on Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1, extranodal sites ≥ 1, and NLR ≥ 4 between groups. There was a higher proportion of patients with high-intermediate and high-risk disease in the learning than in the validation cohort based on IPI and NCCN-IPI scores.

ROC Analysis

The ROC analysis was performed using data from the learning cohort. The optimal NLR cutoff was 4.1, with sensitivity and specificity at optimal cutoff of 40% and 77%, respectively, and the

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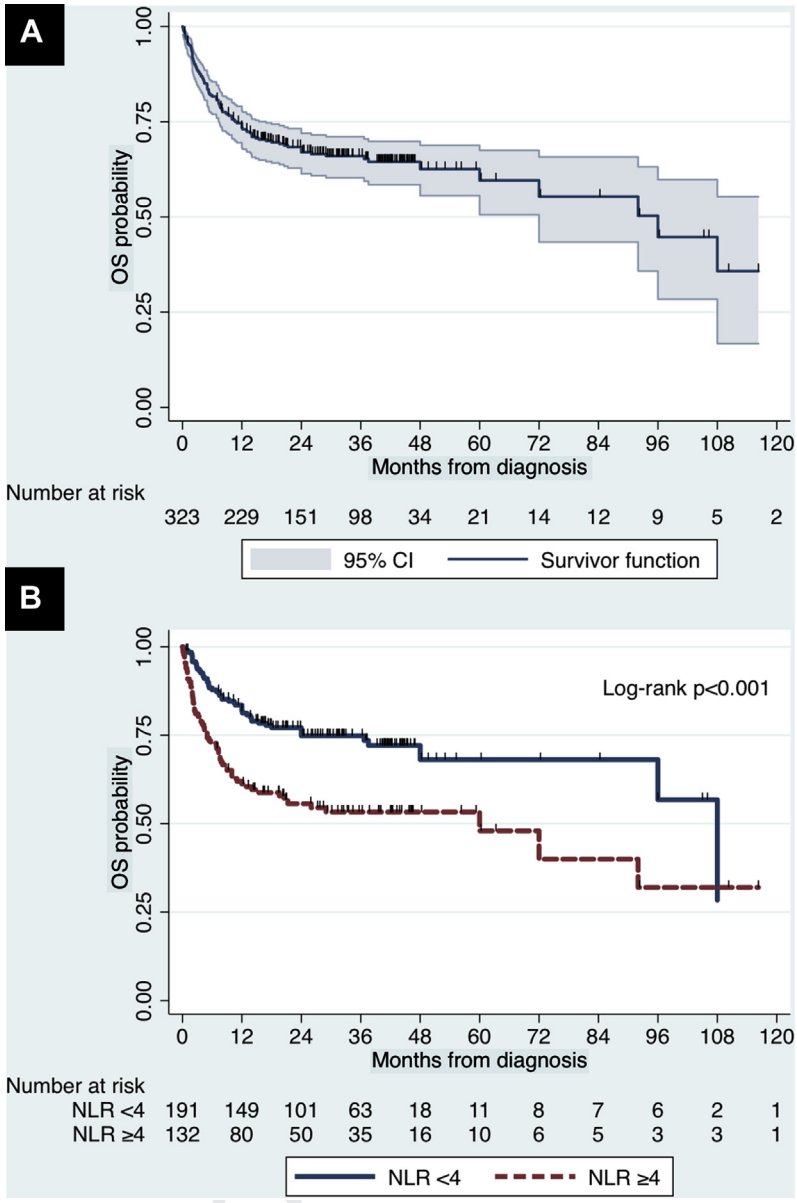
Figure 2 Kaplan-Meier Curves for Overall Survival for the Entire Cohort (A) and by Neutrophil-To-Lymphocyte Ratio (Validation Cohort) (B)



Abbreviations: CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival.

area under the curve (AUC) was 0.58. In the validation cohort, the optimal cutoff was 3.9, with sensitivity and specificity at optimal cutoffs of 55% and 67%, respectively, and an AUC of 0.61. When evaluating the entire cohort, the optimal cutoff was 4, with sensitivity and specificity of 50% and 60%, and an AUC of 0.59. We therefore proceeded with our predictive and prognostic analyses using NLR as a binary variable (NLR $\geq$ 4 and NLR $<$ 4).

Response to Therapy

There was no detectable difference in CR rates between the learning and validation cohorts, as shown in Table 1. Univariate and multivariate logistic regression models for CR to therapy are shown in Table 2. In the univariate analysis, advanced stage and NLR $\geq$ 4 were associated with lower odds of CR in the learning cohort, and elevated LDH, extranodal site $\geq$ 1, advanced stage, and NLR $\geq$ 4 were associated with lower odds of CR in the validation cohort. In the multivariate analysis, advanced stage and NLR $\geq$ 4 were independent predictors of lower rates of CR in the learning cohort, and elevated LDH level and NLR $\geq$ 4 were independent predictors of lower rates of CR in the validation cohort. NLR $\geq$ 4 was an independent predictor of lower rates of CR when adjusting for the IPI and the NCCN-IPI scores in both the learning (OR, 0.46; 95%

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Table 3 Univariate and Multivariate Cox Proportional Hazard Regression Analysis for Overall Survival in Learning and Validation Cohorts

	Univariate Analysis		Multivariate Analysis	
Learning Cohort	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age ≥ 60 y	1.19 (0.78-1.83)	.42	1.16 (0.75-1.79)	.51
ECOG ≥ 1	1.68 (1.10-2.57)	.02	1.57 (1.00-2.42)	.05
Elevated LDH level	1.57 (0.94-2.64)	.09	1.48 (0.87-2.50)	.15
≥ 1 extranodal site	1.69 (0.97-2.95)	.06	1.03 (0.56-1.91)	.91
Stage III or IV	2.50 (1.61-3.88)	<.001	2.47 (1.55-3.93)	<.001
NLR ≥ 4	1.57 (1.04-2.37)	.03	1.55 (1.02-2.36)	.04
	Univariate Analysis		**Multivariate Analysis**	
Validation Cohort	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age ≥ 60 y	1.20 (0.83-1.74)	.34	1.35 (0.92-1.97)	.12
ECOG ≥ 1	2.19 (1.47-3.26)	<.001	1.85 (1.24-2.77)	.003
Elevated LDH level	1.74 (1.20-2.54)	.004	1.16 (0.78-1.73)	.46
≥ 1 extranodal site	2.24 (1.46-3.44)	<.001	1.51 (0.96-2.37)	.07
Stage III or IV	2.45 (1.58-3.81)	<.001	2.04 (1.28-3.26)	.003
NLR ≥ 4	2.09 (1.43-3.30)	<.001	1.80 (1.22-2.65)	.003

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio.

CI, 0.27-0.79; $P = .005$ and OR, 0.47; 95% CI, 0.28-0.81; $P = .006$, respectively) as well as in the validation cohort (OR, 0.46; 95% CI, 0.26-0.82; $P = .008$ and OR, 0.46; 95% CI, 0.25-0.81; $P = .007$, respectively).

Survival Analysis

With a median follow-up time of 62 months, there were 92 (31%) deaths in the learning cohort, and with a median follow-up time of 32 months, there were 112 (35%) deaths in the validation cohort. The 5-year OS rate was 64% (95% CI, 58%-70%) and 60% (95% CI, 51%-68%) in the learning (Figure 1A) and validation cohorts (Figure 2A), respectively. In the learning cohort, 5-year OS rates for NLR < 4 and NLR ≥ 4 were 69% (95% CI, 61%-76%) and 58% (95% CI, 48%-66%), respectively ($P = .03$) (Figure 1B). In the validation cohort, 5-year OS rates for NLR < 4 and NLR ≥ 4 were 75% (95% CI, 68%-81%) and 48% (95% CI, 35%-60%), respectively ($P < .001$) (Figure 2B).

Univariate and multivariate Cox proportional-hazard regression models for OS are shown in Table 3. In the univariate analysis, ECOG performance status ≥ 1, advanced stage, and NLR ≥ 4 were associated with worse OS in the learning cohort, and ECOG performance status ≥ 1, elevated LDH level, extranodal sites ≥ 1, advanced stage, and NLR ≥ 4 were associated with worse OS in the validation cohort. In the multivariate analysis, advance stage and NLR ≥ 4 were independent factors associated with worse OS in the learning cohort, and ECOG performance status ≥ 1, advanced stage, and NLR ≥ 4 were independent factors associated with worse OS in the validation cohort. In the learning cohort, NLR ≥ 4 was an independent prognostic factor for worse OS when adjusting for the IPI score (hazard ratio [HR], 1.50; 95% CI, 1.01-2.28; $P = .04$) and the NCCN-IPI score (HR, 1.47; 95% CI, 1.01-2.21; $P = .04$). In the validation cohort, NLR ≥ 4 was an independent prognostic factor for worse OS when adjusting for the IPI score (HR, 1.81; 95% CI, 1.24-2.64; $P = .002$) and the NCCN-IPI score (HR, 1.96; 95% CI, 1.34-2.86; $P = .001$).

To better understand the discerning role of NLR ≥ 4, we analyzed the impact of this marker in OS outcomes of all patients with DLBCL, including both learning and validation cohorts, stratified by IPI and NCCN-IPI risk categories. In patients with low and low-intermediate IPI score (n = 366), NLR ≥ 4 was associated with lower 5-year OS rate than NLR < 4 (65%; 95% CI, 56%-73% vs. 77%; 95% CI, 69%-83%), and also with higher risk of death from any cause (HR, 1.87; 95% CI, 1.24-2.84; $P = .003$) (Figure 3A). In patients with high and high-intermediate IPI score (n = 224), NLR ≥ 4 was associated with lower 5-year OS rate than NLR < 4 (39%; 95% CI, 29%-50% vs. 52%; 95% CI, 41%-62%), and also with higher risk of death from any cause (HR, 1.56; 95% CI, 1.08-2.27; $P = .02$) (Figure 3B). In patients with low and low-intermediate NCCN-IPI score (n = 292), NLR ≥ 4 was associated with lower 5-year OS rate than NLR < 4 (65%; 95% CI, 53%-74% vs. 79%; 95% CI, 70%-85%) and also with higher risk of death from any cause (HR, 2.20; 95% CI, 1.34-3.59; $P = .002$) (Figure 3C). In patients with high and high-intermediate NCCN-IPI score (n = 300), NLR ≥ 4 was associated with lower 5-year OS rate than NLR < 4 (46%; 95% CI, 37%-55% vs. 56%; 95% CI, 47%-65%) and also with higher risk of death from any cause (HR, 1.45; 95% CI, 1.04-2.03; $P = .03$) (Figure 3D).

Discussion

DLBCL is the most common NHL subtype worldwide.[1] In Latin America, DLBCL is also the most common subtype of NHL.[2] The IPI was established in 1993 and has been one of the most important prognostic tools to stratify patients according to their expected survival.[4] More recently, a novel prognostic score, the NCCN-IPI, was developed, which seems to have a better predictive value for identifying subgroup of patients at "very high" and "very low" risk,[5]

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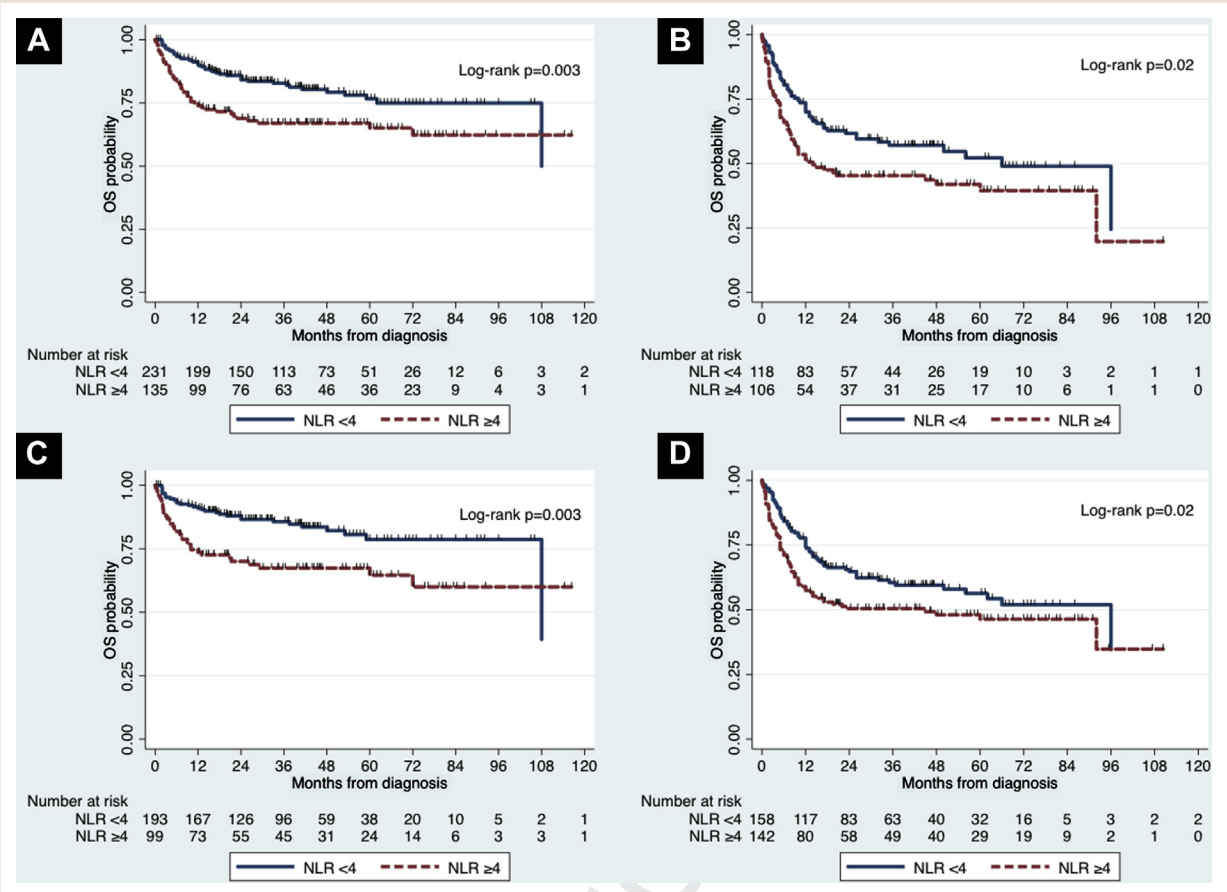
Figure 3 Kaplan-Meier Estimates for Overall Survival According to Neutrophil-To-Lymphocyte Ratio in Patients With DLBCL With Low and Low-Intermediate IPI Score (A), High and High-Intermediate IPI Score (B), Low and Low-Intermediate NCCN-IPI Score (C), and High and High-Intermediate NCCN-IPI Score (D)



Abbreviations: CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; IPI = International Prognostic Index; NCCN IPI = National Comprehensive Cancer Network International Prognostic Index; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival.

probably owing to a more granular stratification of age (ie, < 40 years, 41-59 years, 60-74 years, and > 75 years) and LDH levels (ie, < 1, 1.1-2.9, and > 3 times the upper limit of normal). Nonetheless, all traditional variables in the described prognostic scores have a direct relationship with tumor burden and rate of proliferation (ie, stage, LDH, and extranodal involvement), as well as the biological characteristics of the patient per se (ie, age and performance status).

However, other mechanisms (and potential biological biomarkers) have been suggested as the hallmarks of cancer, such as tumorigenesis and survival advantage.[17] One of these hallmarks is inflammation. In 1863, Rudolf Virchow described the connection between neoplastic cells and inflammation, where inflammation begins as a local process and subsequently becomes systemic. Good examples are hematologic malignancies (eg, Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma), in which the neoplastic lymphocyte is surrounded by a milieu of inflammatory cells that, in turn, has a direct influence in the neoplastic cell survival.[18-20] From the concept of a local-to-systemic inflammatory process, a high expression of different cytokines secreted by the tumor microenvironment, such as interleukin (IL)-6, IL-8, IL-10, interferon gamma, and vascular endothelial growth factor, have been described in DLBCL.[21]

A recent report showed that CXCL-10 is secreted by inflammatory cells of the tumor microenvironment, which increases cell proliferation, as well as cell migration and neoplastic infiltration.[22] Those cytokines are capable of inhibiting lymphocyte and/or stimulating neutrophil production. Thus, different authors have reported that low ALC is associated with a lower response in patients treated with R-CHOP.[23,24] Apparently, the subgroup of lymphocytes depleted with poor outcomes are $CD4^+$ T-lymphocytes.[26,27] Meanwhile, the loss of stimulation and expansion of cytotoxic $CD8^+$ T-lymphocytes and NK cells have a direct relation with the control of neoplastic cells.[28] Other authors have reported that high ANC was associated with shorter survival and proposed neutrophilia as a key mediator of malignant transformation, tumor progression, angiogenesis, and antitumor immunity modulation through their release of soluble factors (cytokines or chemokines) or their interaction with tumor cells.[29,30] Hirz et al showed in preclinical models that neutrophils and neoplastic B-cells interact

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Table 4 Previous Studies That Have Evaluated the Neutrophil-to-Lymphocyte Ratio in Patients With DLBCL Treated With Chemoimmunotherapy

Author, Year	Country	No. Cases	Treatment Regimen	NLR Cutoff (Method)	5-year OS (%) ≥ Cutoff	HR (95% CI)
Beltran & Villela, 2020	GELL	597	R-CHOP	4 (ROC)	Learning: 58%	1.55 (1.02-2.36)
					Validation: 48%	1.80 (1.22-2.65)
Annibali, 2019[42]	RELLI	505	R-CHOP and R-CHOP-like	Per Porrata et al	64% (4-year OS)	1.83 (1.15-2.91)
Azuma, 2019[41]	Japan	530	R-CHOP	5.2 (Q2)	52%	1.38 (0.98-1.94)
Wang, 2018[40]	China	182	R-CHOP	2.32 (ROC)	78% (2-year OS)	NR
Go, 2018[39]	Korea	232	R-CHOP	6 (Cutoff finder-web[a])	30%	NR
Beltran, 2018[38]	Peru	121	R-CHOP	6 (Q3)	46%	2.68 (1.31-5.47)
Wang, 2017[37]	China	355	R-CHOP	2.81 (ROC)	54%	1.66 (1.04-2.74)
Hong, 2017[22]	Korea	313	R-CHOP	2.42 (Q2)	NR	NR
Wang, 2016[36]	China	156	R-CHOP	3 (ROC)	57.5%	3.3 (1.6-7)
Ho, 2015[30]	Taiwan	148	R-CHOP	4.35 (ROC)	58%	2.31 (1.32-4.57)
Melchardt, 2015[35]	Austria	482	R-CHOP	5.54 (ROC)	NR	1.14 (0.79-1.6)
Keam, 2015[34]	Korea	447	R-CHOP	3 (Q2)	66.7% (2-year OS)	1.54 (1.06-2.24)
Troppan, 2015[33]	Austria	290	R-CHOP	4 (ROC)	53%	2.03 (1.17-3.5)
Porrata, 2010[32]	USA	255	R-CHOP	3.5 (Q2)	56%	NR ($P < .03$)

Abbreviations: CI = confidence interval; GELL = Grupo de Estudio Latinoamericano de Linfoproliferativos; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; NR = not reported; OS = overall survival; Q2 = interquartile 50; Q3 = interquartile 75; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ROC = receiver operating characteristic.
[a] ■■■. Q6

through their CD11b and ICAM-1 receptors, respectively, activating the MCL-1 pathway, perpetuating the life of the neoplastic lymphocyte, and presenting resistance to cytotoxic agents.[31]

Therefore, biological evidence supports that low ALC and high ANC are directly related to inflammation and could be used as biomarkers in DLBCL. However, it is currently unclear if the NLR can be used as a prognostic biomarker in DLBCL, because the current clinical data have produced conflicting results.[22,30,32-41] Table 4 shows a systematic review of published studies evaluating NLR in DLBCL. Two recent systematic reviews and meta-analyses have suggested the NLR as an adverse prognostic factor in DLBCL.[44,45] However, the inclusion criteria, as well as the NLR cutoff used in the studies included, were heterogeneous, and therefore these analyses are prone to bias. None of these studies used ROC analysis to differentiate risk groups. Other studies estimated the NLR cutoff using quartiles.

We designed a retrospective study aimed at evaluating the NLR in 2 separate cohorts of Latin American patients with a diagnosis of DLBCL. To the best of our knowledge, this is the largest study to date on evaluating the prognostic value of this easy-to-use biomarker in DLBCL. The learning and validation cohorts of the GELL study have a few differences in demographic characteristics. The learning cohort had a higher proportion of elderly patients and increased LDH level as well as a higher proportion of high-risk patients in both IPI and NCCN-IPI scores than the validation cohort. Despite this difference in baseline characteristics, no difference in CR rates (72% and 74%, respectively) and 5-year OS rates (64% and 60%, respectively) were observed between the learning and the validation cohorts. Both the IPI and the NCCN-IPI scores were prognostic in both learning and validation cohorts, which we believe provide validity and consistency to our results.

The strength of our study is based on 3 aspects. First, we use a strong methodology such as the use of the ROC analysis, which is based on sensitivity and specificity as well as positive and negative predictive values and is considered the gold standard for determination of cutoff levels in biological biomarkers.[25] Second, we performed our analysis in a learning cohort from several South American countries, and later validated the results with an independent population from Central America (Mexico). This is the largest study done as a cooperative effort in Latin America. And third, our cohorts, as expected, not only are clinically, ethnically, and biologically heterogeneous, they also include patients treated in different settings (eg, academic and community centers). Despite the inherent heterogeneity expected in our cohorts, the NLR showed to be a robust adverse biomarker for survival in patients with DLBCL treated with chemoimmunotherapy. Finally, the NLR could add on the prognostic value of well-known and commonly used prognostic scores such as the IPI and NCCN-IPI.

We acknowledge that our study has limitations. This study is retrospective and could have suffered from selection bias. Hence, studies should be developed that prospectively evaluate the NLR. Being a retrospective study, we could not evaluate and correlate with other biomarkers such as C-reactive protein, chemokines, or interleukins. On the other hand, obtaining these inflammatory biomarkers would represent a high financial cost for patients and health care systems in Latin America. In this context, extramural research opportunities could represent an important source for funding for the study of lymphomas in Latin America. Similarly, we could not classify our patients as double hit or double expressors, as these data were not uniformly obtained in all participating centers. Finally, there are missing data in our cohorts. However, the missing data appeared to be at random and comprises less than 10% of our observations.

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In conclusion, the NLR could become a useful and inexpensive prognostic inflammatory biomarker for DLBCL. This is of key importance in countries with limited resources and also limited access to sophisticated diagnostic platforms or expensive reagents. Therefore, biomarkers with commonly used laboratory workup take an important role in our population.

Clinical Practice Points

- An NLR of 4 or higher was independently associated with lower odds of CR and higher risk of death in Latin American patients with DLBCL treated with R-CHOP.
- The adverse prognostic value of NLR of 4 or higher was independent of the IPI and the NCCN-IPI score.
- The NLR can be used to further refine the prognosis of patients with DLBCL treated with chemoimmunotherapy in areas with limited resources.

Acknowledgments

LV received support from Fondo Sectorial de Investigación en Salud y Seguridad Social SSA/IMSS/ISSSTE-CONACYT-2012-C01-180096, México.

Disclosures

LV received honoraria from Abbvie, Amgen, Astra Zeneca, Celgene, Roche, and Takeda (Mexico). CP received honoraria from Janssen, Novartis, Roche and Tecnofarma (Chile). HI received honoraria from Alexion, Amgen, Astra Zeneca, Janssen, Novartis, Novo Nordisk, PTC Pharmaceuticals, Recordati Rare Disease, Roche, Sanofi, Strennus Pharmaceutical, and Takeda (Colombia). SP received honoraria from Tecnofarma (Peru). IP received honoraria from Bayer, Novo Nordisk and Roche (Colombia). ARI has received fees from Abbvie and Roche (Mexico). JJC has received research funding and/or consulting fees from Abbvie, Beigene, Janssen, Kymera, Pharmacyclics, and TG Therapeutics (USA). All other authors state that they have no conflicts of interest.

Uncited Reference

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