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Research paper

The impact of the neutrophil:lymphocyte ratio in response and survival of patients with de novo diffuse large B-cell lymphoma

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ABSTRACT

The neutrophil:lymphocyte ratio (NLR) has emerged as prognostic in patients with hematological malignancies. We aimed at evaluating the NLR as predictive for complete response (CR) and prognostic for progression-free (PFS) and overall survival (OS) in a study cohort of 121 Peruvian patients with diffuse large B-cell lymphoma (DLCBL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Patients with an NLR ≥6 (n = 28) were more likely to have a performance status ECOG ≥2 (74% vs. 23%; p < 0.001). NLR ≥6 was associated with lower CR rate to R-CHOP (46% vs. 74%; p = 0.02) and there was a trend towards significance in multivariate regression analyses (OR 0.36, 95% CI 0.11–1.00; p = 0.05). Patients with NLR ≥6 had lower 5-year PFS rate (39% vs. 72%; p < 0.001) and lower 5-year OS rate (46% vs. 75%; p = 0.001) than patients with NLR < 6 and was an independent adverse factor for PFS (HR 2.43, 95% CI 1.21–4.87; p = 0.01) and OS (HR 2.68, 95% CI 1.31–5.47; p = 0.007) in multivariate Cox regression analyses. NLR ≥6 was prognostic of PFS and OS after adjusting for the International Prognostic Index and the NCCN-IPI scores. In conclusion, the NLR could add predictive and prognostic value to well established prognostic tools in DLBCL.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype in the world [1]. DLBCL is also the most common lymphoma as well in Latin American countries [2]. In Peru specifically, DLBCL represents up to 66% of all cases of lymphoma [3]. The response and survival of patients with DLBCL are highly variable and a number of prognostic tools have been developed for this purpose. The most commonly used prognostic models for DLBCL are the International Prognostic Index (IPI) score and the International Prognostic Improvement Index (NCCN-IPI) [4,5]. However, no prognostic tool is perfect, and additional research is needed to further refine our prognostic capabilities.

The neutrophil:lymphocyte ratio (NLR) has been evaluated as an adverse prognostic factor in different types of malignancies, such as breast cancer, lung cancer, hepatocarcinoma and pancreatic cancer [6–10]. In hematological malignancies, the NLR also appears useful in predicting prognosis in patients with myeloma, peripheral T-cell lymphoma and DLBCL [11–13]. In our country, there is no study evaluating NLR as a prognostic factor in DLBCL.

We hypothesized that the NLR would be of predictive and prognostic value for response and survival, respectively, in adult patients with DLBCL. We therefore designed a retrospective study to evaluate such hypothesis, and to also evaluate the value of the NLR after adjusting for the IPI and NCCN-IPI scores.

2. Patients and methods

2.1. Patient selection

The present study corresponds to an observational, transversal, analytical and retrospective design. The study population corresponded to all patients diagnosed with DLBCL between January 2010 and December 2012 at the Department of Medical Oncology of the Edgardo Rebagliati Martins Hospital in Lima, Peru. Inclusion criteria were histopathological diagnosis of DLBCL, patients older than 18 years, complete clinical information and follow-up, and having received treatment with rituximab, cyclophosphosphamide, doxorubicin, vincristine and prednisone (R-CHOP) at standard doses with a curative intent. Exclusion criteria were HIV infection, transformation from indolent

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lymphoma, and central nervous system or leukemic involvement by DLBCL at diagnosis.

2.2. Data gathering

Relevant clinical and pathological data were gathered, which included but were not limited to age, sex, performance status, clinical stage, extranodal sites of involvement, lactate dehydrogenase (LDH) levels, presence of B symptoms, response to therapy and overall survival. For purposes of this study, absolute neutrophil and lymphocyte counts at the time of DLBCL diagnosis were also collected. The NLR was estimated by dividing the absolute neutrophil count over the absolute lymphocyte count. Response to therapy was assessed using standard criteria, whenever possible.[29] Progression-free survival (PFS) was defined as the time between diagnosis and progression of disease, last follow-up or death from any cause. Overall survival (OS) was defined as the time between diagnosis and last follow-up or death from any cause.

2.3. Statistical analysis

Clinicopathological data are presented using descriptive statistics, and characteristics between groups compared using Chi-square. Univariate and multivariate regression models were fitted to evaluate the association of clinical variables and complete response to therapy. For the survival analysis, the Kaplan-Meier method was used to generate PFS and OS curves, which were compared using the log-rank test. The Cox regression method was used to establish univariate and multivariate survival models for PFS and OS. The outcome of interest was reported as the Hazard Ratio (HR) with 95% Confidence Interval (CI) of progression or death from any cause and death from any cause, respectively. P-values < 0.05 were considered significant. Calculations and graphs were obtained using STATA version 14 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patients' characteristics

A total of 121 patients with DLBCL treated with R-CHOP were included in our analysis. The clinical characteristics of the patients are shown in Table 1. The median NLR was 3.5, interquartile range (IQR) 2.3–6. Based on the IQR, patients were divided in 4 categories (category 1: NLR 0–2.2, category 2: NLR 2.3–3.4, category 3: NLR 3.5–5.9, category 4: NLR 6 or higher). Patients with NLR of 6 or higher were more likely to have an ECOG performance status of 2 or higher (74% vs. 23%; $p < 0.001$). There was a trend in patients with NLR of 6 or higher of having higher rates of elevated LDH levels (74% vs. 54%; $p = 0.06$) and also higher rates of high-intermediate (39% vs. 29%) and high risk NCCN-IPI scores (36% vs. 19%; $p = 0.09$).

3.2. Response to R-CHOP

The CR rate in the entire cohort was 68%. DLBCL patients with NLR of 6 or higher had a lower CR rate than patients with NLR lower than 6 (46% vs. 74%, $p = 0.02$; Table 1). In the univariate logistic regression analysis, ECOG of 2 or higher, elevated LDH, stage III/IV and NLR of 6 or higher were significantly associated with lower rate of CR. In a multivariate model including these four factors, NLR of 6 or higher was the stronger factor associated with lower CR rate (OR 0.36, 95% CI 0.11–1.00; $p = 0.05$). The univariate and multivariate models are shown in Table 2. The IPI score also associated with CR. Low-intermediate, high-intermediate and high IPI score had an OR for CR of 0.42 (95% CI 0.13–1.42; $p = 0.16$), 0.30 (95% CI 0.09–1.02; $p = 0.05$) and 0.13 (95% CI 0.04–0.44; $p = 0.001$), respectively, using low IPI as the reference group. NLR of 6 or higher remained statistically significant after adjusting for the IPI (OR 0.36, 95% CI 0.14–0.91; $p = 0.03$). The NCCN-IPI did not associate with CR. Low-intermediate, high-intermediate and high NCCN-IPI had OR for CR of 1.21 (95% CI 0.21–6.97; $p = 0.83$), 0.66 (95% CI 0.12–3.74; $p = 0.64$) and 0.30 (95% CI 0.05–1.79; p-0.19; $p = 0.19$), respectively, using low NCCN-IPI as the reference group. NLR of 6 or higher also remained significantly associated with lower CR rates after adjusting for NCCN-IPI (OR 0.37, 95% 0.15–0.93; $p = 0.03$).

Table 1
Baseline characteristics of 121 patients with DLBCL treated with R-CHOP according to NLR.

	Total (n = 121)	NLR < 6 (n = 93)	NLR 6+ (n = 28)	p-value
Age 60+ years	81 (67%)	63 (68%)	18 (64%)	0.73
Male sex	54 (45%)	41 (44%)	13 (46%)	0.82
ECOG 2+	41 (34%)	21 (23%)	20 (74%)	< 0.001
Elevated LDH	70 (58%)	50 (54%)	20 (74%)	0.06
2+ extranodal sites	69 (57%)	54 (58%)	15 (54%)	0.67
Stage III/IV	50 (41%)	39 (42%)	11 (39%)	0.80
B symptoms	72 (60%)	53 (57%)	19 (68%)	0.30
IPI score				
Low risk	42 (35%)	36 (39%)	6 (21%)	0.14
Low-intermediate risk	28 (23%)	23 (25%)	5 (18%)	
High-intermediate risk	25 (21%)	16 (16%)	9 (32%)	
High risk	26 (21%)	18 (19%)	8 (29%)	
NCCN-IPI score				
Low risk	9 (7%)	8 (9%)	1 (4%)	0.09
Low-intermediate risk	46 (38%)	40 (43%)	6 (21%)	
High-intermediate risk	38 (31%)	27 (29%)	11 (39%)	
High risk	28 (23%)	18 (19%)	10 (36%)	
Response to therapy				
Complete response	82 (68%)	69 (74%)	13 (46%)	0.02
Partial response	14 (12%)	9 (10%)	5 (19%)	
No response	25 (21%)	15 (16%)	10 (36%)	

NLR: neutrophil-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; IPI: International Prognostic Index; NCCN: National Comprehensive Cancer Network.

Table 2
Univariate and multivariate logistic regression models for complete response in 121 patients with DLBCL treated with R-CHOP.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age 60+ years	1.68 (0.76–3.73)	0.20		
Male sex	0.78 (0.36–1.69)	0.53		
ECOG 2+	0.29 (0.13–0.64)	0.002	0.78 (0.28–2.19)	0.64
Elevated LDH	0.25 (0.10–0.62)	0.003	0.41 (0.15–1.11)	0.08
2+ extranodal sites	0.76 (0.35–1.65)	0.49		
Stage III/IV	0.34 (0.15–0.75)	0.007	0.43 (0.12–1.06)	0.07
B symptoms	0.45 (0.20–1.03)	0.06		
NLR 6+	0.30 (0.13–0.72)	0.007	0.36 (0.11–1.00)	0.05

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

3.3. Progression-free survival

The median follow-up for the entire group was 5.6 years (95% CI 5.4–6 years). There was no difference in follow-up between groups based on NLR. The median follow-up in the group with NLR of 6 or higher was 5.9 years (95% CI 4.9–6.5) versus 5.6 years (95% CI 5.3–6 years) in patients with NRL lower than 6 (log-rank $p = 0.39$). The median PFS was 6.6 years (95% CI 5.5–not reached; Fig. 1**A**). In the univariate analysis, ECOG of 2 or higher, elevated LDH level, stage III/

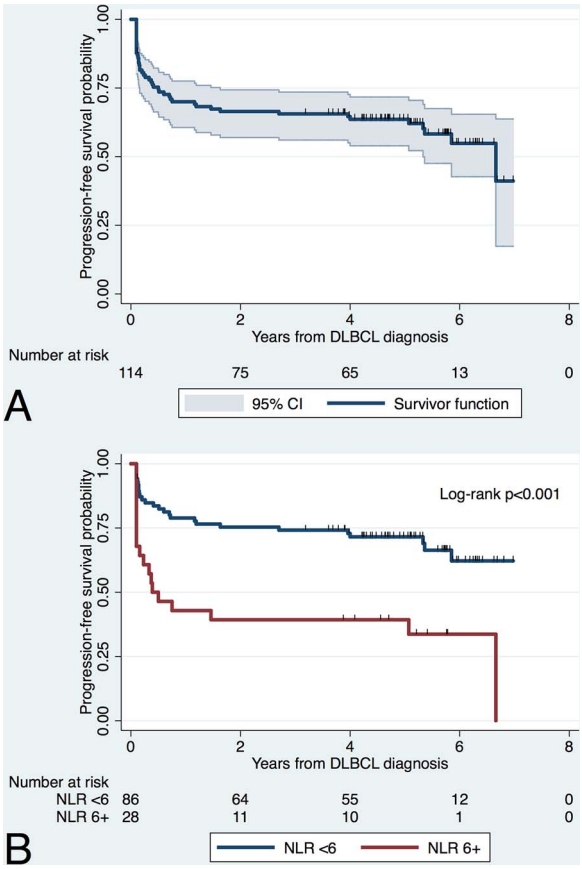

Fig. 1. Progression-free survival estimates in 114 patients with DLBCL treated with R-CHOP for the entire cohort (A), and according to the NLR (B).

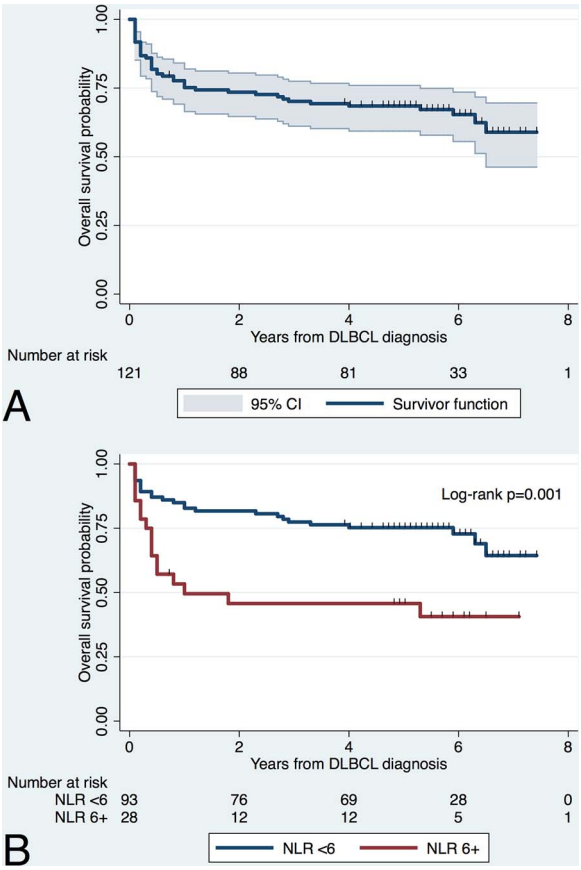

Fig. 2. Overall survival estimates in 121 patients with DLBCL treated with R-CHOP for the entire cohort (A), and according to the NLR (B).

Table 3
Univariate and multivariate Cox proportional-hazard regression models for progression-free and overall survival in patients with DLBCL treated with R-CHOP.

PFS (n = 114)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age 60+ years	1.11 (0.58–2.11)	0.76		
Male sex	0.80 (0.44–1.46)	0.48		
ECOG 2+	1.85 (1.41–2.43)	< 0.001	1.37 (0.97–1.94)	0.08
Elevated LDH	2.62 (1.36–5.08)	0.004	1.50 (0.73–3.10)	0.27
2+ extranodal sites	0.98 (0.55–1.76)	0.95		
Stage III/IV	2.29 (1.26–4.16)	0.006	1.46 (1.05–2.03)	0.02
B symptoms	1.60 (0.87–2.94)	0.13		
NLR 6+	2.98 (1.65–5.39)	< 0.001	2.43 (1.21–4.87)	0.01
OS (n = 121)	**Univariate analysis**		**Multivariate analysis**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age 60+ years	1.49 (0.75–2.97)	0.26		
Male sex	0.94 (0.51–1.73)	0.84		
ECOG 2+	2.82 (1.53–5.19)	0.001	1.48 (0.72–3.02)	0.28
Elevated LDH	2.55 (1.28–5.08)	0.008	1.63 (0.78–3.39)	0.20
2+ extranodal sites	0.93 (0.51–1.72)	0.83		
Stage III/IV	2.67 (1.44–4.96)	0.002	2.59 (1.34–5.00)	0.004
B symptoms	1.23 (0.66–2.29)	0.52		
NLR 6+	2.69 (1.43–5.03)	0.002	2.68 (1.31–5.47)	0.007

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

IV and NLR of 6 or higher were associated with a worse OS. The 5-year PFS rate in patients with NLR of 6 or higher was lower than in patients with NLR lower than 6 (39% vs. 72%; log-rank p < 0.001; Fig. 1**B**). In a multivariate model including ECOG, LDH level, stage and NLR, ECOG of 2 or higher, stage III/IV and NLR of 6 or higher were independently associated with a worse PFS. Univariate and multivariate Cox regression models are shown in Table 3 **(top)**. The IPI and the NCCN-IPI score were associated with PFS (log-rank p < 0.001 for both indexes). NLR of 6 or higher was independently associated with worse PFS after adjusting by the IPI score (HR 2.54, 95% CI 1.38–4.66; p = 0.003) and the NCCN-IPI score (HR 2.31, 95% CI 1.26–4.24; p = 0.007).

3.4. Overall survival

At the time of this report, 43 patients have died, of which 30 (70%) died of progression of disease, 10 (23%) from infectious complications, and 3 (7%) of other causes. The median OS was 10.5 years (95% CI 6.5-not reached; Fig. 2**A**). In the univariate analysis, ECOG of 2 or higher, elevated LDH level, stage III/IV and NLR of 6 or higher were associated with a worse OS. The 5-year OS rate in patients with NLR of 6 or higher was lower than in patients with NLR lower than 6 (46% vs. 75%; log-rank p = 0.001; Fig. 2**B**). In a multivariate model including ECOG, LDH level, stage and NLR, only stage III/IV and NLR of 6 or higher were independently associated with a worse OS. Univariate and multivariate Cox regression models are shown in Table 3 **(bottom)**. The IPI score and the NCCN-IPI score were associated with OS (log-rank p < 0.001 for both indexes). NLR 6 or higher was independently associated with a worse OS after adjusting for the IPI score, (HR 2.36, 95% CI 1.23–4.51; p = 0.009), and the NCCN-IPI score (HR 2.10, 95% CI 1.10–4.00; p = 0.03).

4. Discussion

Our retrospective study suggests that NLR of 6 of higher can be

prognostic of PFS and OS, and possibly predictive of CR in adult patients de novo DLBCL treated with R-CHOP. Additionally, the prognostic value of NLR of 6 or higher is independent of the IPI and NCCN-IPI scores.

Biologically, the NLR can serve as an easy-to-measure-and-use tool reflecting on two distinct but otherwise intertwined processes in DLBCL: a systemic inflammatory response and lymphopenia. Previous studies have shown that a systemic inflammatory response is protumoral [14]. An increase in number of neutrophils mediated by the inflammatory response favors tumor angiogenesis and may negatively influence the activity of specific subtypes of T-lymphocytes [15,16]. Furthermore, there is biological, clinical and epidemiological data associating chronic inflammation and antigenic stimulation with the development of lymphomas [17–20]. Lymphopenia probably reflects a generalized depressed immune activity, and correlates with poor prognosis in lymphoma, myeloma and leukemia [21–25]. Immunodeficiency has also been associated with an increased risk of developing lymphomas, such as in HIV infection and post-transplant states [26,27].

Given the mounting evidence on the potential prognostic value of the NLR in DLBCL patients, a meta-analysis was recently executed and published [28]. This meta-analysis combined the results of 9 studies including over 2000 patients with DLBCL. However, the study lacked uniformity in the cutoff of NLR used and had an overrepresentation of Asian studies. Seven studies were from China, Korea and Taiwan, 1 study was from the United States and 1 study from Europe. In all, data on the prognostic value of the NLR are lacking in Latin American patients. To the best of our knowledge, this is the first study validating the prognostic value of the IPI score, the NCCN-IPI score and of the NLR (with a cutoff of 6 or higher as an adverse marker) in a Latin American population. The findings of a predictive value for the IPI and NCCN-IPI scores in our study cohort provide validity to our study on further supporting the independent prognostic value of the NLR.

Our study, however, is not without weaknesses. The study cohort was composed of Peruvian patients, which could argue against the generalization of our findings to other ethnicities. However, we could argue that our findings could be generalizable to other Latin American countries, and that the NLR has already shown to be prognostic in Caucasian and Asian populations. One could argue that our study cohort was small, composed of 121 patients. However, our patients were consecutively selected and all the patients were uniformly treated with standard doses of R-CHOP with a curative intent. Additionally, there was long enough follow-up time of about 5 years to estimate a reliable survival in these patients. Another potential weakness is the retrospective nature of our design. We addressed this issue not only by selecting consecutive patients but also by using a carefully designed case report form, which minimized missing data. Furthermore, our analyses fitted statistical models fully adjusted for relevant clinical factors associated with prognosis in DLBCL patients.

We firmly believe our findings should be independently validated in other Latin American populations. Recently, a number of Latin American investigators have formed the Latin American Group for the Study of Lymphoma (GELL), which besides providing a platform to support and run prospective clinical trials, it can also provide a mechanism to design and execute meaningful epidemiological and clinical research in patients with lymphoma from Latin American countries.

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