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# The neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with peripheral T-cell lymphoma, unspecified

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## Abstract

Peripheral T-cell lymphoma (PTCL) encompasses a group of rare and aggressive lymphomas. PTCL, unspecified (PTCLU) is the most common subtype of PTCL, and carries a poor prognosis. The International Prognostic Index (IPI) and the Prognostic Index for PTCLU (PIT) scoring systems are powerful risk-stratification tools in patients with PTCL. The aim of this study was to evaluate whether the neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor in PTCLU. We retrospectively studied 83 patients with diagnosis of PTCLU. In the univariate analysis,  $NLR \geq 4$  was associated with worse overall survival (HR 3.96, 95% CI 1.92–8.17;  $p < 0.001$ ). In the multivariate analysis,  $NLR \geq 4$  was independently associated with worse overall survival after adjustment for the PIT score (HR 4.30, 95% CI 1.90–9.69;  $p < 0.001$ ), and for the IPI score (HR 2.60, 95% CI 1.12–6.04;  $p = 0.03$ ). Our study suggests the NLR could be helpful in refining the survival prognostication in patients with PTCLU.

**Keywords:** lymphopenia, neutrophil, neutrophil-to-lymphocyte ratio, peripheral T-cell lymphoma, unspecified, PTCL, prognostic factor

## Introduction

Peripheral T-cell lymphoma (PTCL) is comprised of a heterogeneous group of disorders characterized by the malignant proliferation of mature T-lymphocytes. PTCL, unspecified (PTCL-U) is the most common subtype of PTCL seen worldwide, and is associated with a 5-year overall survival (OS) of approximately 30% [1]. Several studies have evaluated potential prognostic factors for OS in patients with PTCL. Among the most commonly used tools are the International Prognostic Index (IPI) and the Prognostic Index for PTCL-U (PIT) scoring systems [2,3]. However, new prognostic

biomarkers might be helpful in refining risk-stratification in PTCL patients.

A previous study from our group showed that lymphopenia was an important prognostic factor for OS in patients with a PTCL-U, which was independent from the PIT score [4]. More recently, the neutrophil-to-lymphocyte ratio (NLR) has been identified as an independent prognostic factor for OS and progression-free survival (PFS) in several types of solid tumors such as non-small cell lung cancer, colorectal cancer, cholangiocarcinoma, hepatocellular carcinoma, breast cancer and pancreatic cancer [5–11]. The NLR has also been suggested as a prognostic factor in patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP [12,13].

However, the role of the NLR as a prognostic factor for OS in patients with PTCL-U has not been evaluated. Our main objective was to evaluate the prognostic value for OS of the NLR in patients with PTCL-U.

## Methods

### Case selection

From January 1998 to December 2012, consecutive patients with a pathological diagnosis of PTCL-U were identified from the medical records at the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru. Pathological samples were retrieved, and reviewed by three expert hematopathologists (CA, DM and PQ), and reclassified, if necessary, according to the 2008 World Health Organization (WHO) Classification of Tumors of the Haematopoietic and Lymphoid Tissues. Patients younger than 18 years or with pathological diagnosis of a different, specified systemic PTCL, such as adult T-cell leukemia/lymphoma, anaplastic large cell lymphoma, angioimmunoblastic lymphoma or natural killer/T-cell lymphoma, were excluded. Patients with primary cutaneous PTCL variants were also excluded. All patients received treatment with

anthracycline-based combination chemotherapy. The study protocol was reviewed and approved by the Hospital Nacional Edgardo Rebagliati Martins' Institutional Review Board.

### Data gathering

Clinical data were gathered from the medical records of the selected patients. Clinical parameters included age, gender, B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH) levels, hemoglobin levels, number of extranodal sites, bone marrow involvement by lymphoma, Ann Arbor clinical stage, IPI score, PIT score, final outcome, and OS in months. The NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC) at PTCL-U diagnosis. We divided the cohort into two groups:  $NLR \geq 4$  and  $NLR < 4$  based on the cutoff used in a recent meta-analysis [14].

### Statistical analysis

Clinicopathological data are presented using descriptive statistics. Continuous variables were dichotomized to facilitate analysis. The Chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. Response assessment was performed based on criteria presented elsewhere. Logistic regression was used to evaluate the association between clinical factors and response. Results of the logistic regression analyses are presented as odds ratio (OR) with 95% confidence interval (CI). OS was defined as the time in months between date of diagnosis and the date of last follow-up or death. For the survival analysis, the Kaplan-Meier method was used to generate univariate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit multivariate survival models. Results of the Cox models are reported as hazard ratio (HR) with 95% CI. All reported *p*-values are two-sided, and were considered significant if less than 0.05. Calculations and graphics were obtained using the statistical software STATA version 13.1 (College Station, Texas, USA).

### Results

A total of 93 patients were found in our database. From these, NLR data were missing in ten (11%), and they were excluded from the analysis. There were no differences, however, in any of the variables analyzed between the excluded and the included patients. Therefore, 83 patients were finally included in our study. The patients' characteristics are shown in Table I. The median age at presentation was 58 years (range 18–87 years). The median hemoglobin level was 11.2 g/dl (range 5.9–15.5 g/dl), the median ANC was  $3.6 \times 10^9/L$  (range  $0.6\text{--}58.4 \times 10^9/L$ ), the median ALC was  $1.4 \times 10^9/L$  (range  $0.2\text{--}21.2 \times 10^9/L$ ), and the median absolute monocyte count (AMC) was  $0.6 \times 10^9/L$  (range  $0.1\text{--}2.4 \times 10^9/L$ ). The median NLR was 2.5 (range 0.3–99). Patients with PTCL-U who had  $NLR \geq 4$  at diagnosis were more likely to be men, to present with advanced stage (i.e. stage III or IV), to have elevated LDH levels, and to have high-risk IPI scores. There were no differences between the NLR groups with regards to age, performance status, number of extranodal sites,

Table I. Patients' characteristics according to neutrophil-to-lymphocyte ratio.

	Total (%)	NLR < 4 (%)	NLR ≥ 4 (%)	<i>p</i> -value
Total	83 (100)	54 (65%)	29 (35%)	-
Age				
< 60 years	47 (57)	30 (56)	17 (59)	0.82
≥ 60 years	36 (43)	24 (44)	12 (41)	
Sex				
Female	41 (49)	32 (59)	9 (31)	0.01
Male	42 (51)	22 (41)	20 (69)	
Performance				
Good	46 (57.5)	33 (65)	12 (45)	0.58
Poor	34 (42.5)	18 (35)	12 (57)	
Stage				
Early (I or II)	25 (31)	22 (42)	3 (11)	0.01
Advanced (III or IV)	55 (69)	31 (58)	24 (89)	
LDH level				
Normal	42 (56)	33 (66)	9 (36)	0.03
Elevated	33 (44)	17 (34)	16 (64)	
Extranodal sites				
0–1 sites	67 (83)	45 (85)	22 (79)	0.54
> 1 sites	14 (17)	8 (15)	6 (21)	
Bone marrow				
Uninvolved	56 (71)	35 (66)	21 (81)	0.20
Involved	23 (29)	18 (34)	5 (19)	
B symptoms				
Absent	27 (33)	20 (38)	7 (24)	0.23
Present	55 (67)	33 (62)	22 (76)	
IPI score				
Low risk (0–2 factors)	46 (60)	37 (73)	9 (35)	< 0.01
High risk (3–5 factors)	31 (40)	14 (27)	17 (65)	
PIT score				
Low risk (0–2 factors)	61 (79)	43 (83)	18 (72)	0.37
High risk (3–4 factors)	16 (21)	9 (17)	7 (28)	
Response				
Complete	34 (42.5)	25 (47)	9 (33)	0.33
Partial	8 (10)	6 (11)	2 (7)	
No response	38 (47.5)	22 (42)	16 (59)	

NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PIT, Prognostic Index for peripheral T-cell lymphoma, unspecified.

bone marrow involvement, hemoglobin levels, PIT score or response to therapy.

With regard to treatment, 74 patients received combination chemotherapy (89%), and 9 patients (11%) received radiotherapy alone or steroids without chemotherapy or were not treated. Fifty patients (68%) were treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and 24 (32%) with CHOP and etoposide (CHOEP). Response was assessed in 70 patients with complete response (CR) seen in 42.5%, partial response (PR) in 10% and no response in 47.5% of patients. In the univariate logistic regression analysis, advanced stage (OR 0.27, 95% CI 0.11–0.68; *p* = 0.005), high LDH levels (OR 0.31, 95% CI 0.12–0.82; *p* = 0.02) and poor performance status (OR 0.23, 95% CI 0.09–0.63; *p* = 0.004) were associated with lower odds of achieving CR. NLR was not associated with achieving CR.

In the univariate survival analysis, poor performance status, advanced stage, elevated LDH level, > 1 extranodal site, presence of B symptoms and  $NLR \geq 4$  were associated with worse OS (Figure 1A). Also, a high IPI score (HR 4.31, 95% CI 2.05–9.04; *p* < 0.001; Figure 1B) and a high PIT score (HR 4.47, 95% CI 2.01–9.94; *p* < 0.001; Figure 1C) were associated with worse OS. In the multivariate analysis,  $NLR \geq 4$  was associated with a worse outcome after adjusting for performance status, LDH level, number of extranodal sites and

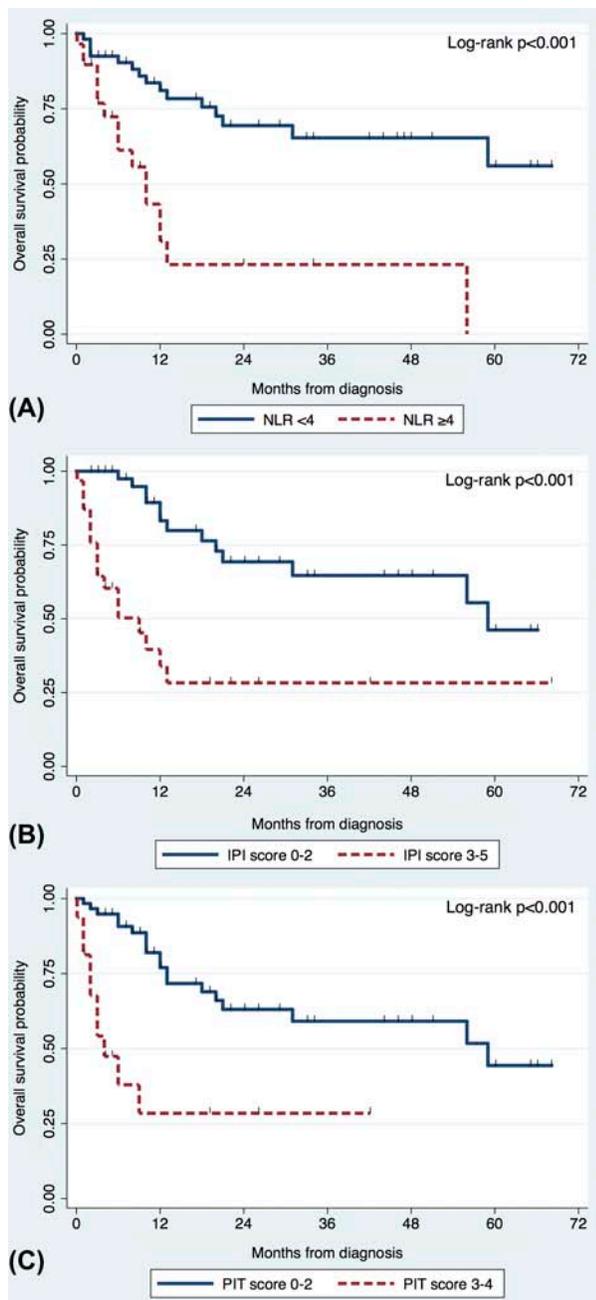


Figure 1. Overall survival estimates in 83 patients with peripheral T-cell lymphoma, unspecified (PTCL-U), according to (A) neutrophil-to-lymphocyte ratio, (B) International Prognostic Index, and (C) Prognostic Index for PTCL-U.

B symptoms. The univariate and multivariate OS Cox models are shown in Table II.

When analyzed side-by-side, both high IPI score (HR 3.58, 95% CI 1.66–7.73;  $p = 0.01$ ) and  $NLR \geq 4$  (HR 3.32, 95% CI 1.52–7.25;  $p = 0.003$ ) were associated with a worse outcome. Similarly, when analyzed side-by-side, both high PIT score (HR 4.66, 95% CI 2.02–10.7;  $p < 0.001$ ) and  $NLR \geq 4$  (HR 4.32, 95% CI 1.96–9.51;  $p < 0.001$ ) were associated with worse outcome. In a multivariate model adjusting simultaneously for both the IPI and the PIT scores,  $NLR \geq 4$  remained significantly associated with a worse OS (HR 3.94, 95% CI 1.75–8.84;  $p = 0.001$ ) while the IPI score (HR 2.38, 95% CI 0.87–6.48;  $p = 0.09$ ) and the PIT score (HR 2.46, 95% CI 0.86–7.00;  $p = 0.09$ ) were not significant. In stratified analyses,  $NLR \geq 4$

Table II. Univariate and multivariate analysis for overall survival in 83 patients with peripheral T-cell lymphoma, unspecified.

	Univariate		Multivariate	
	HR (95% CI)	$p$ -value	HR (95% CI)	$p$ -value
Age				
Younger than 60	1.00			
60 years or older	0.90 (0.44–1.85)	0.78		
Sex				
Female	1.00			
Male	0.99 (0.49–2.00)	0.97		
Performance				
Good	1.00		1.00	
Poor	6.36 (2.93–13.8)	< 0.01	4.93 (1.88–12.9)	0.01
Stage				
Early (I or II)	1.00		1.00	
Advanced (III or IV)	2.88 (1.16–7.12)	0.02	0.75 (0.24–2.28)	0.61
LDH level				
Normal	1.00		1.00	
Elevated	2.45 (1.17–5.14)	0.02	1.13 (0.47–2.73)	0.78
Extranodal sites				
0–1 sites	1.00		1.00	
> 1 sites	2.62 (1.16–5.91)	0.02	1.25 (0.48–3.27)	0.65
Bone marrow				
Uninvolved	1.00			
Involved	1.53 (0.72–3.23)	0.27		
B symptoms				
Absent	1.00		1.00	
Present	8.16 (1.95–34.2)	< 0.01	3.30 (0.69–15.7)	0.13
NLR				
4 or higher	1.00		1.00	
Less than 4	4.30 (2.05–9.01)	< 0.01	4.73 (1.78–12.6)	< 0.01

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

was associated with HR 2.28 (95% CI 0.80–6.50;  $p = 0.12$ ) in patients with high IPI score and HR 2.94 (95% CI 0.88–9.79;  $p = 0.08$ ) in patients with low IPI score. Also,  $NLR \geq 4$  was associated with HR 2.58 (95% CI 0.60–11.1;  $p = 0.20$ ) in patients with high PIT score and HR 3.98 (95% CI 1.55–10.2;  $p = 0.004$ ) in patients with low PIT score.

To further validate our findings, we evaluated the AMC using a cutoff of  $AMC > 0.5 \times 10^9/L$  as an adverse factor based on previous studies in mantle cell lymphoma [15] and extranodal natural killer cell lymphoma [16]. An  $AMC > 0.5 \times 10^9/L$  was seen in 64% of our patients and was not associated with OS (HR 0.54, 95% CI 0.22–1.31;  $p = 0.18$ ). We also calculated the lymphocyte-to-monocyte ratio (LMR), by dividing the ALC over the AMC.  $LMR \leq 3$  was seen in 47% of our patients, and was considered an adverse prognostic factor based on a previous study in patients with diffuse large B-cell lymphoma (DLBCL) [17].  $LMR \leq 3$  was not associated with OS (HR 1.01, 95% CI 0.43–2.40;  $p = 0.98$ ). We also evaluated lymphopenia, defined as  $ALC < 1.0 \times 10^9/L$ , as an adverse prognostic factor given our previous experience [4]. Lymphopenia was seen in 36% of our patients and was associated with OS in the univariate analysis (HR 3.69, 95% CI 1.77–7.69;  $p < 0.001$ ). When analyzing NLR and lymphopenia side-by-side, lymphopenia was not associated with OS (HR 2.05, 95% CI 0.74–5.65;  $p = 0.17$ ). There was a trend towards significance for  $NLR \geq 4$  (HR 2.49, 95% CI 0.89–6.98;  $p = 0.08$ ).

## Discussion

To the best of our knowledge, this study represents the first formal evaluation of the NLR as a prognostic factor for

survival in PTCL-U. PTCL is a rare type of lymphoma in the US and Europe, accounting for approximately 10–15% of the cases; however, the incidence is higher in countries such as Peru, in which PTCL accounts for approximately 20% of all lymphomas [1,19]. Interestingly, the rate of PTCL in Peru appears higher than in other South American countries such as Argentina or Brazil [20]. The reasons behind this difference have not been entirely elucidated.

In general, patients with PTCL have worse outcomes than patients with DLBCL [21]. PTCL encompasses several lymphoma subtypes, of which PTCL-U is the most common [1,22]. PTCL-U usually develops in the fifth or sixth decade of life, and has no sex predilection. PTCL-U presents advanced disease with nodal compromise as well as skin, liver, spleen, bone marrow and peripheral blood involvement. B symptoms occur in 45% of cases at diagnosis [22–24]. The prognosis is rather poor with OS rates of 30% at 5 years with current therapeutic approaches [1].

The IPI and the PIT scores are prognostic indexes commonly used to risk-stratify patients with aggressive lymphomas. Although the PIT score appears specific for patients with PTCLU, the prognostic value of the IPI score has also been validated in patients with PTCL [25]. The IPI score is composed by five clinical variables (i.e. age, performance status, LDH levels, extranodal involvement and stage) [2], and the PIT score by four (i.e. age, performance status, LDH levels and bone marrow involvement) [3]. According to these variables, patients with PTCL-U can be risk-stratified in groups with better or worse prognosis. The survival of patients with PTCL-U can vary greatly depending on these variables. Other prognostic tools include the clinicopathological prognostic index, in which Ki-67 expression was added to other clinical factors (i.e. age, performance status and LDH level) [26], and the International Peripheral T-cell lymphoma Project score (IPTCLP), which includes age, performance status and platelet counts [27]. Overall, there is an ongoing need for further refinement of the prognosis of patients with PTCL with reliable and easy-to-use markers.

The NLR has been previously evaluated as an adverse prognostic factor in patients with cancers of the breast, lung, liver, colon, and pancreas. More recently, Templeton *et al.* showed in a meta-analysis that included over 40,000 patients with a diversity of solid tumors that the NLR was associated with an adverse OS [14]. In hematologic malignancies, Porrata *et al.* showed that NLR was a prognostic factor in patients with DLBCL treated with R-CHOP, and recently, a study by Keam *et al.* has confirmed such findings [12,13]. A variant called “derived” NLR was also prognostic in DLBCL [28]. The “derived” NLR is calculated by dividing the difference between absolute leukocyte count and absolute neutrophil count over the absolute neutrophil count.

The NLR index might reflect two separate but interrelated processes, the systemic inflammatory response and the status of the immune system. Current evidence suggests systemic inflammatory processes help tumor progression [29]. Tumor progression is induced by inflammatory cells mediating biological mechanisms such as release of growth and survival factors, promotion of angiogenesis and lymphangiogenesis, stimulation of DNA damage and promotion

of immune evasion [30]. Also, inflammatory cells such as tumor-associated macrophages have been associated with poor prognosis in lymphomas. These M2 macrophages have a Th2 immune pattern with host immunity suppression [31]. Our study showed that neither the AMC nor the LMR were prognostic of survival in patients with PTCLU.

Lymphopenia, on the other hand, might reflect a depressed specific antitumor immune activity. Lymphopenia has been associated with poor prognosis in solid tumors as well as hematologic malignancies such as Hodgkin lymphoma, myeloma, acute leukemia and DLBCL [32–38]. Our group previously reported that lymphopenia carried an adverse prognosis in patients with PTCL-U [4]. These findings were later reproduced by a larger study by the IPTCLP [39]. Lymphopenia was also prognostic of survival in our cohort but lost its significance when evaluated against the NLR. This finding, along with the lack of significance of the AMC and LMR, suggests a necessary existing interaction between inflammation and immunodeficiency.

Our study suggests that NLR at diagnosis is a prognostic factor in patients with PTCL-U. High NLR (> 4) was present in 35% of our patients and was associated with male sex, advanced stage, increased LDH, and high risk IPI score. This ratio appears to be a useful and inexpensive prognostic factor in PTCL-U. Our study, understandably, has several limitations such as the small number of patients, potential selection bias and its retrospective nature. However, we believe these results warrant further investigation in larger retrospective as well as prospective studies.

In conclusion, our study shows that NLR is a prognostic factor for survival in patients with a diagnosis of PTCL-U, and appears independent from the PIT and IPI scores. Prognostic factors are a necessary part of our risk-stratification tools, as they would help clinicians set appropriate goals for therapy and carry survival discussions.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article at [www.informahealthcare.com/lal](http://www.informahealthcare.com/lal).

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