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Lymphopenia as a prognostic factor in patients with peripheral T-cell lymphoma, unspecified

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Abstract
Peripheral T-cell lymphoma, unspecified (PTCLU) is the most common T-cell lymphoma variant. The molecular heterogeneity of PTCLU is reflected by a diverse clinical course. Several prognostic factors have been studied, but further refinement is needed. The aim of our study was to retrospectively evaluate the presence of lymphopenia, defined as a lymphocyte count of < 1000 cells/mm^3, as a prognostic factor for survival in patients with PTCLU. Sixty-nine cases with a pathological diagnosis of PTCLU were included in our analysis. Lymphopenia was seen in 38% of the patients and was statistically associated with a worse response to chemotherapy. In univariate analysis, lymphopenia, IPI score > 2, and Prognostic Index for PTCLU (PIT) score > 2 were associated with a worse overall survival. In multivariate analysis, lymphopenia and a PIT score > 2 were the only independent poor prognostic factors, implying an important role of the patient's immune system in both response to therapy and survival.

Keywords: *Peripheral T-cell lymphoma, unspecified, PTCLU, lymphopenia, prognostic factors*

Introduction

Peripheral T-cell lymphomas (PTCLs) are rare disorders characterized by the malignant proliferation of mature (peripheral) T-lymphocytes. PTCL, unspecified (PTCLU) is the most common subtype of PTCL, accounting for 26% of all cases, although variations in its incidence have been noted according to geographical location [1]. PTCLU is characterized by a heterogeneous morphology and molecular profile [2], akin to diffuse large B-cell lymphoma (DLBCL), the most common variant of lymphoma of B-cell origin [3]. However, in contrast to DLBCL, there is no standardized approach to the treatment of PTCL [1]. Furthermore, the heterogeneity of PTCLU translates into a highly diverse clinical course and prognosis.

Some studies have evaluated potential prognostic factors for survival in patients with PTCL. To name two, the International Prognostic Index (IPI) and the Prognostic Index for PTCLU (PIT) scores have been developed and retrospectively evaluated [1,4]. However, more refined prognostic tools are necessary to risk-stratify our patients more appropriately, improve our understanding of the biology of the disease, and therefore improve our therapies. As a matter of fact, several reports have associated lymphopenia with worse survival in patients with different malignancies, such as Hodgkin and non-Hodgkin lymphomas (HL and NHL, respectively), sarcomas, and breast carcinomas [5,6]. However, the role of lymphopenia as a prognostic factor for overall survival (OS) in patients with PTCLU has not been evaluated.

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The primary objective of our study was to retrospectively evaluate the presence of lymphopenia, defined as an absolute lymphocyte count (ALC) of <1000 cells/mm^3, as a prognostic factor for OS in patients newly diagnosed with PTCLU. A secondary objective was to compare the clinical characteristics of patients with PTCLU according to their ALC.

Patients and methods

Case selection

From January 1998 to December 2007, patients with a pathological diagnosis of PTCLU were identified at the Hospital Nacional Edgardo Rebagliati Martins, in Lima, Peru. Pathological samples were retrieved, reviewed by two expert hematopathologists (D.M. and P.Q.), and reclassified, if necessary, according to the 2008 World Health Organization (WHO) 'Classification of tumors of the haematopoietic and lymphoid tissues' [3]. 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 nasal natural killer (NK)/T-cell lymphoma, were excluded. Patients with primary cutaneous PTCL variants were also excluded. 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 (>60 or ≤ 60 years), gender (male or female), B symptoms (present or absent), Eastern Cooperative Oncology Group (ECOG) performance status (<2 or ≥ 2), lactate dehydrogenase (LDH) levels (normal or elevated), hemoglobin levels (<10 or ≥ 10 g/dL), albumin levels (<3.5 or ≥ 3.5 g/dL), β_2-microglobulin levels (<3.4 or ≥ 3.4 mg/L), number of extranodal sites (>1 or ≤ 1), bone marrow involvement by lymphoma (present or absent), Ann Arbor clinical stage (early [1 and 2] or advanced [3 and 4]), ALC (<1000 or ≥ 1000 cells/mm^3), IPI score (low [1 and 2] or high [3 and 4]), PIT score (low [1 and 2] or high [3 and 4]), administration of chemotherapy (yes or no), response to chemotherapy (complete [CR], partial [PR], or no [NR]), final outcome (dead or alive), and OS in months.

Statistical analysis

Clinicopathological data are presented using descriptive statistics. Continuous variables were dichotomized, as shown above, to facilitate their analysis. The χ^2 test was used to compare clinical characteristics between groups according to the ALC. OS was defined as the lapse of time in months between the date of diagnosis and the date of last follow-up or death. For univariate survival analysis, the Kaplan–Meier method for incomplete observations was used. The estimated survival curves were compared using the log-rank test. The Cox proportional-hazard regression method was used to perform multivariate survival analysis. 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 MedCalc, version 11.3.3.0 (Mariakerke, Belgium).

Results

General characteristics

The main clinical characteristics of the 69 patients included in our study are shown in Table I. The median follow-up for the entire group was 24 months (range 1–66 months). The median age was 58 years (range 24–87 years), with a slight male predominance with a male-to-female ratio of 1.2:1. The median lymphocyte count was 1350 cells/mm^3 (range 59–27 518 cells/mm^3), and the median hemoglobin level was 10.9 g/dL (range 5.9–15.5 g/dL). The median albumin level was 3.1 g/dL (range 1.9–4.8 g/dL), and the median β_2-microglobulin level was 3.2 mg/L (range 1–27.7 mg/L). With regard to the IPI score, 14 (25%), 12 (22%), 16 (29%), and 13 (24%) patients had low, low-intermediate, high-intermediate, and high risk scores, respectively. In regard to the PIT score, seven (13%), 14 (26%), 15 (28%), and 18 (33%) patients had scores of 0, 1, 2 and 3–4 points, respectively.

Thirty-seven patients (54%) from our cohort received chemotherapy. The majority of the remaining 32 patients (46%) were not treated due to a poor performance status or rapid progression of the disease. In fact, 21 of these patients (66%) died within 30 days of their initial diagnosis. From the 37 patients who underwent chemotherapy, 32 patients (86%) received CHOP-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Response data were available in 36 patients (97%); the overall response rate was 61%, with a CR rate of 47% and a PR rate of 14%; no response to chemotherapy was seen in 39% of patients. At the time of this report, 37 patients (54%) had deceased, the large majority (76%) due to lymphoma progression.

Lymphopenia in PTCLU

The incidence of lymphopenia in the studied population was 38%. A comparison of the clinical

Table I. General characteristics and univariate overall survival analysis of 69 patients with a diagnosis of PTCLU.

Characteristic	Number (%)	Median OS (months)	HR (95% CI)	*p*-Value
Age				
Older than 60	33 (48%)	10	1.3 (0.7–2.6)	0.34
Younger than 60	36 (52%)	13	1.0	
Performance status				
ECOG >1	34 (53%)	2	3.4 (1.8–6.7)	<0.0001
ECOG <2	30 (47%)	59	1.0	
LDH level				
Elevated	33 (57%)	3	2.6 (1.3–5.3)	0.006
Normal	25 (43%)	NR	1.0	
Extranodal sites				
>1 site	15 (22%)	10	1.2 (0.5–2.8)	0.59
0–1 site	54 (78%)	10	1.0	
Clinical stage				
Advanced	45 (65%)	10	1.4 (0.8–2.8)	0.24
Early	24 (35%)	20	1.0	
Bone marrow involvement				
Positive	16 (23%)	10	1.1 (0.5–2.2)	0.93
Negative	53 (77%)	13	1.0	
Presence of B symptoms				
Positive	46 (67%)	10	1.4 (0.7–3.0)	0.29
Negative	23 (33%)	20	1.0	
Hemoglobin level				
<10 g/dL	23 (34%)	5	1.7 (0.8–3.6)	0.10
≥10 g/dL	45 (66%)	20	1.0	
Albumin level				
<3.5 g/dL	24 (63%)	3	2.1 (0.9–4.9)	0.10
≥3.5 g/dL	14 (37%)	20	1.0	
β_2-Microglobulin level				
≥3.4 mg/L	18 (46%)	3	1.5 (0.6–3.8)	0.33
<3.4 mg/L	21 (54%)	12	1.0	
IPI score				
Score 3–4	36 (54%)	3	2.9 (1.5–5.9)	0.0001
Score 1–2	31 (46%)	59	1.0	
PIT score				
Score 3–4	34 (51%)	3	3.2 (1.6–6.7)	0.0001
Score 1–2	32 (49%)	59	1.0	
Absolute lymphocyte count				
<1000 cells/mm^3	26 (38%)	1	3.3 (1.6–6.9)	<0.0001
≥1000 cells/mm^3	43 (62%)	59	1.0	

PTCLU, peripheral T-cell lymphoma, unspecified; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PIT, Prognostic Index for PTCLU; HR, hazard ratio; CI, confidence interval; NR, not reached.

Table II. Comparison of clinical characteristics according to absolute lymphocyte count (ALC).

Characteristic	ALC ≥1000 cells/mm^3 (*n*)	ALC <1000 cells/mm^3 (*n*)	*p*-Value
Age			
Older than 60	20 (61%)	13 (39%)	0.97
Younger than 60	23 (64%)	13 (36%)	
Performance status			
ECOG >1	20 (59%)	14 (41%)	0.70
ECOG <2	20 (67%)	10 (33%)	
LDH level			
Elevated	17 (52%)	16 (48%)	0.19
Normal	18 (72%)	7 (28%)	
Extranodal sites			
>1 site	9 (60%)	6 (40%)	0.93
0–1 site	34 (63%)	20 (37%)	
Clinical stage			
Advanced	27 (60%)	18 (40%)	0.78
Early	16 (67%)	8 (33%)	
Bone marrow involvement			
Positive	10 (63%)	6 (37%)	0.78
Negative	33 (62%)	20 (38%)	
Presence of B symptoms			
Positive	26 (57%)	20 (43%)	0.25
Negative	17 (74%)	6 (26%)	
Hemoglobin level			
<10 g/dL	14 (61%)	9 (39%)	0.88
≥10 g/dL	28 (62%)	17 (38%)	
Albumin level			
<3.5 g/dL	14 (58%)	10 (42%)	0.65
≥3.5 g/dL	10 (71%)	4 (29%)	
β_2-Microglobulin level			
≥3.4 mg/L	10 (56%)	8 (44%)	0.94
<3.4 mg/L	13 (62%)	8 (38%)	
IPI score			
Score 3–4	20 (56%)	16 (44%)	0.44
Score 1–2	21 (68%)	10 (32%)	
PIT score			
Score 3–4	18 (53%)	16 (47%)	0.18
Score 1–2	23 (72%)	9 (28%)	
Response to chemotherapy			
Complete response	15 (88%)	2 (16%)	0.02*
Partial response	4 (80%)	1 (20%)	
No response	7 (50%)	7 (50%)	

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PIT, Prognostic Index for peripheral T-cell lymphoma, unspecified; ACT, absolute lymphocyte count.
*p-Value for trend.

characteristics of patients with PTCLU according to their ALC is shown in Table II. Lymphopenia was not statistically associated with any clinical variable, such as age, performance status, LDH, hemoglobin, albumin, or β_2-microglobulin level, number of extranodal sites, clinical stage, bone marrow involvement, presence of B symptoms, and IPI or PIT score; however, there was a statistically significant correlation between lymphopenia and a poor response to chemotherapy ($p = 0.02$).

Survival analysis

The median OS for the entire group ($n = 69$) was 10 months [Figure 1(A)]. In univariate analysis (Table I), a high IPI score (score >2), a high PIT score (score >2), and lymphopenia at presentation were associated with a worse OS in patients with PTCLU, with p-values of 0.0001, 0.0001, and <0.0001,

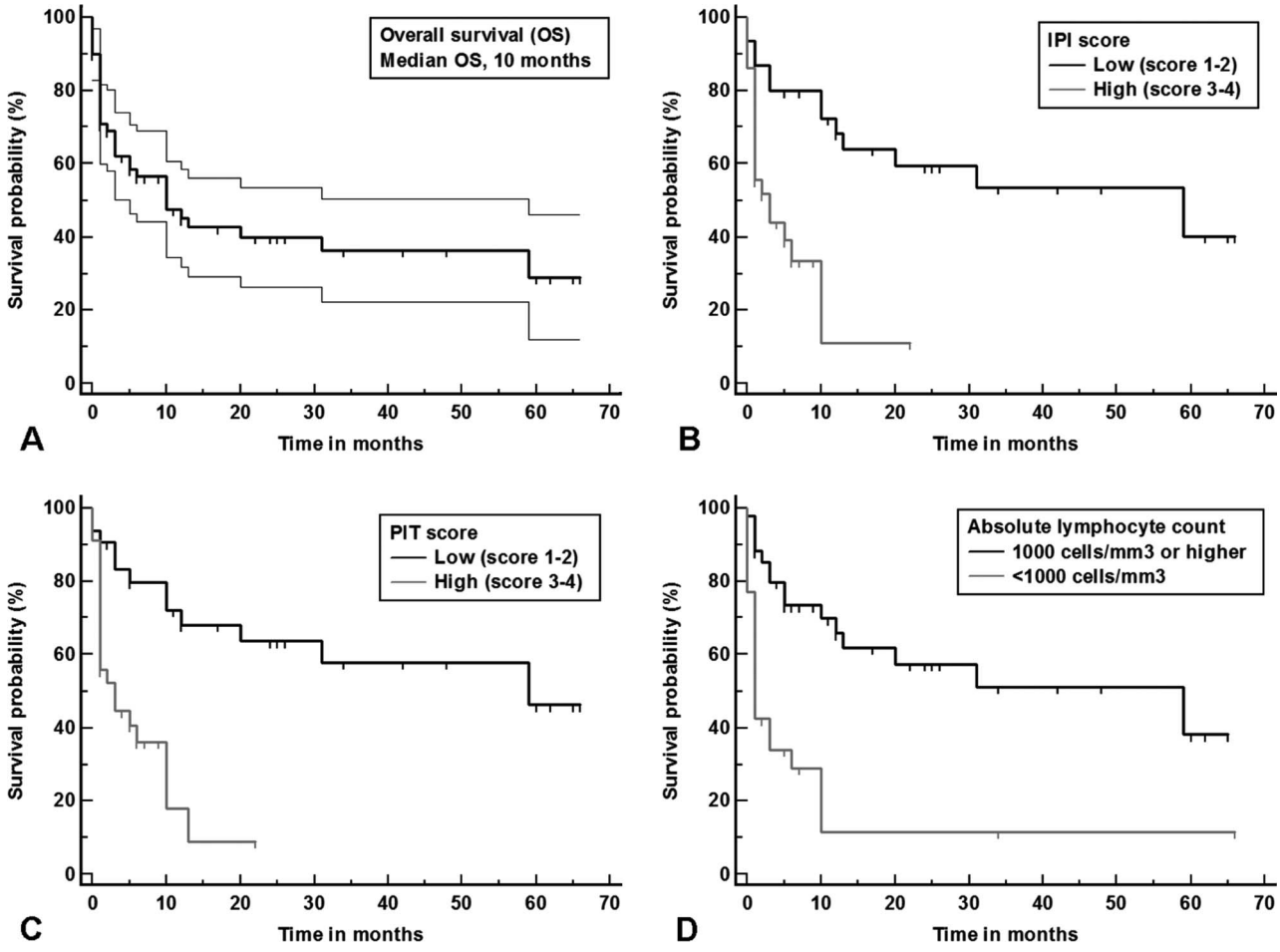

Figure 1. Kaplan–Meier survival estimates in 69 newly diagnosed patients with peripheral T-cell lymphoma, unspecified (PTLCU) for the whole group (A), and according to the International Prognostic Index score (B), Prognostic Index for PTCLU (C), and absolute lymphocyte count (D).

respectively [Figures 1(B), 1(C), and 1(D), respectively]. Hemoglobin levels <10 g/dL and albumin levels <3.5 g/dL showed a statistical trend toward a worse OS ($p=0.10$ each). In multivariate analysis, a high PIT score and lymphopenia at presentation were independent prognostic factors for worse OS, with hazard ratios (HRs) of 4.8 (95% confidence interval [CI] 2.0–11.7) and 4.0 (95% CI 1.9–8.3), respectively.

Patients treated with chemotherapy ($n=37$) had a longer OS than patients not receiving chemotherapy (59 months vs. 1 month, $p<0.0001$) [Figure 2(A)]. In univariate analysis including only patients treated with chemotherapy, a high IPI score, a high PIT score, and lymphopenia at presentation remained associated with a worse prognosis, with p-values of 0.001, 0.0004, and 0.01, respectively [Figures 2(B), 2(C), and 2(D), respectively]. In multivariate analysis, a high PIT score and lymphopenia at presentation were independent poor prognostic factors for OS, with HRs of 9.3 (95% CI 2.2–39.5) and 3.5 (95% CI 1.0–12.0), respectively.

Discussion

PTCLU is the most common subtype of systemic PTCL seen worldwide [1]. Several clinical and pathological factors, such as age, clinical stage, performance status, bone marrow involvement, and Ki-67 expression, have been associated with prognosis, and few prognostic tools have been developed. Gallamini and colleagues developed the PIT score, a prognostic score to risk-stratify patients with PTCLU; the PIT score uses clinical variables (i.e. age, performance status, LDH level, and bone marrow involvement) to subdivide patients into four different risk categories [4]. More recently, Went and colleagues developed a clinicopathological index which has also shown prognostic value, with addition of the immunohistochemical expression of Ki-67 to other clinical factors (i.e. age, performance status, and LDH level) [7]. Given the inherent heterogeneity of PTCLU, it is likely that further refinement is necessary for risk-stratification purposes. Our study adds to the existing body of

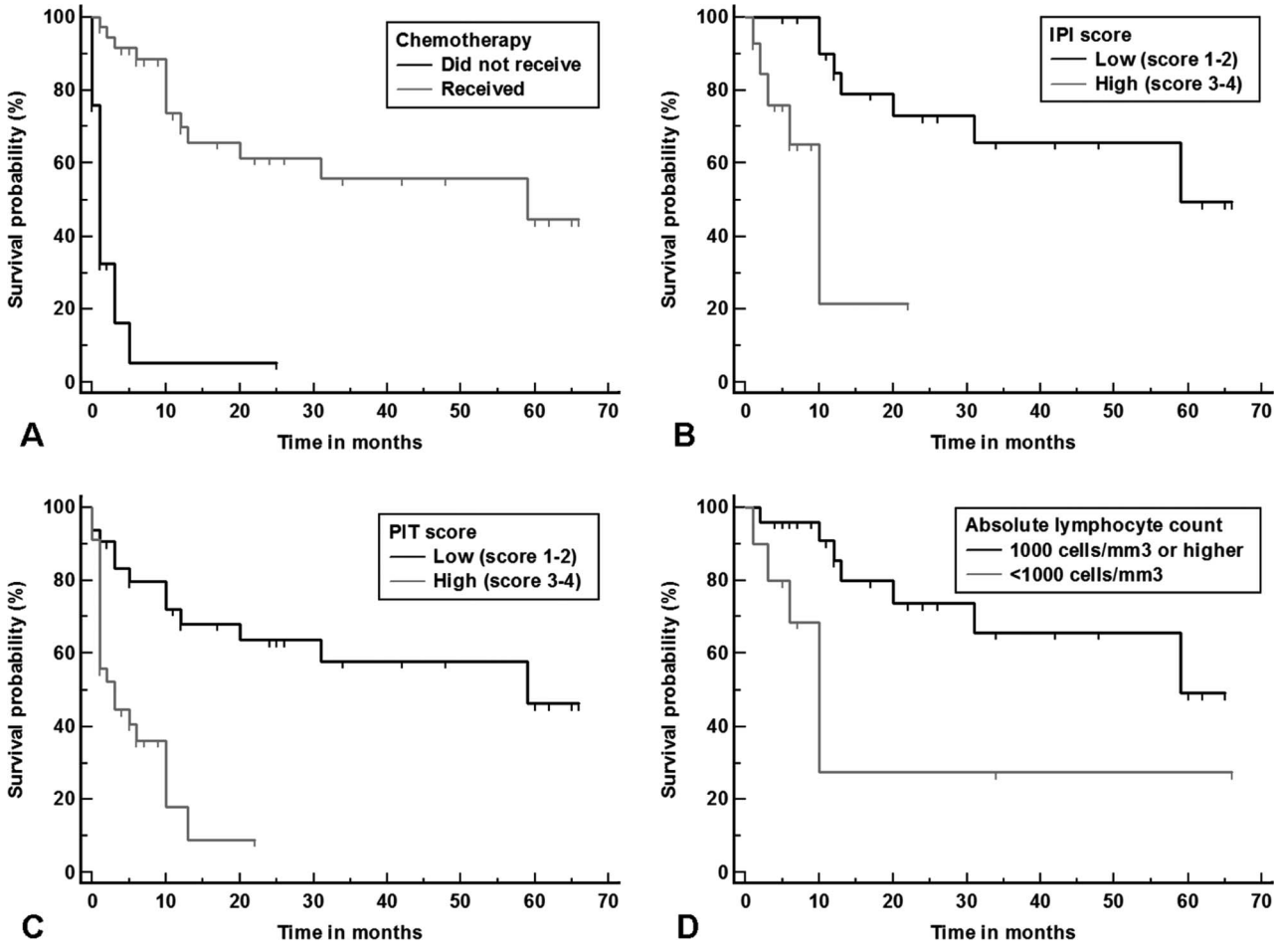

Figure 2. Kaplan–Meier survival estimates in 69 newly diagnosed patients with peripheral T-cell lymphoma, unspecified (PTLCU) according to therapy received (A), and in 37 patients with PTCLU treated with chemotherapy according to the International Prognostic Index score (B), Prognostic Index for PTCLU (C), and absolute lymphocyte count (D).

literature by identifying an easy-to-use prognostic marker such as ALC at presentation, prior to administration of chemotherapy.

The observed incidence of lymphopenia at lymphoma presentation in our population was 38%. This is in concordance with prior reports in other lymphoma subtypes, in which the incidence of lymphopenia has ranged from 20 to 50% [6,8,9]. Interestingly, the highest incidence of lymphopenia was described in a study of patients with a diagnosis of angioimmunoblastic T-cell lymphoma (AITL) [10]. The reasons for this degree of variability are likely multifactorial, since infections, post-surgical state, autoimmune disorders, and use of steroids may play a role; however, the lack of uniformity on the definition of ALC seems to be the most important factor.

Lymphopenia has been associated with poor survival in other lymphoproliferative disorders. In 1998, the International Prognostic Factors Project on Advanced Hodgkin's Disease evaluated over 5000 patients with advanced Hodgkin disease provided from 25 different institutions, and included lymphopenia, defined as an ALC of less than 600 cells/mm^3, as part of their prognostic score [5]. A more recent study evaluated the abovementioned score in 379 patients with Hodgkin lymphoma to predict their survival after autologous stem cell transplant; in this study, lymphopenia was again independently associated with event-free survival (EFS) and OS [11]. However, a smaller study focusing on the prognostic value of ALC in 238 patients with Hodgkin lymphoma at any stage did not find a correlation between lymphopenia and disease-free survival, but the ALC was evaluated as a continuous variable, and no specific cutoff was provided [12]. A more recent study evaluated the role of lymphopenia, defined as ALC <1000 cells/mm^3, in the survival of 165 patients with DLBCL [9]; in a multivariate analysis, lymphopenia was associated with poorer OS, independent of the IPI score. Similarly, Kim and colleagues demonstrated that lymphopenia was an

independent prognostic factor for EFS and OS in 223 patients with DLBCL [13]. More recent studies have found similar results in patients with DLBCL [14,15]. Finally, a large study by Ray-Coquard and colleagues evaluated lymphopenia as a prognostic factor for OS in 802 patients, of whom 322 had NHL [6]. Lymphopenia was an independent prognostic factor for progression-free survival and OS, although no data on NHL subtype were available. Furthermore, lymphopenia has also shown prognostic value in follicular lymphoma, plasma cell myeloma, acute leukemias, and stem cell transplant for hematologic malignancies [16–19]. To our knowledge, this is the first study evaluating lymphopenia as a prognostic factor in PTCLU. Our study shows that lymphopenia, defined as an ALC < 1000 cells/mm^3, is an independent prognostic factor for OS in patients with a diagnosis of PTCLU. This is a novel finding that, we believe, deserves to be further explored.

Reasons for the association between lymphopenia and worse survival observed in patients with PTCLU are currently unclear and, based on the results of this study, deserve further attention. Several theories can explain the above findings. First, lymphopenia has been associated with an increased risk of developing febrile neutropenia during chemotherapy [8], which in turn can adversely affect survival. Unfortunately, the rates of febrile neutropenia were not available in our population. Second, the ALC may be a reflection of the overall immune status of the patient; hence, lymphopenia could be the harbinger of a crippled immune system, which could be associated with worse response to chemotherapy and survival [13]. Our study shows that the only clinical variable associated with lymphopenia was response to chemotherapy, supporting this theory. Third, the depletion or stimulation of specific lymphocyte subsets may be attributed as responsible for worse or improved responses and survival, respectively. For example, Plonquet and colleagues showed that higher absolute NK-cell counts prior to chemotherapy were associated with improved survival in patients with DLBCL enrolled in the LNH988B3 trial of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) [20].

Another area of intense research has focused on the biology and function of regulatory T-cells (T-regs), which would play a transcendental role in tumor immunity. Proper identification and targeting of T-regs could provide clinicians with valuable therapeutic tools against malignancies. We believe the potential prognostic role of lymphopenia in PTCLU is a reflection of the importance of the immune system's role in tumor surveillance. On the same note, multiple biological markers such as albumin level, soluble interleukin-2 receptor (sIL2R) level and CCR4 expression have shown potential prognostic value [21–23]. Our study found a trend for albumin levels < 3.5 g/dL for prognosis ($p = 0.10$), but, unfortunately, we did not evaluate our patients for CCR4 expression or serum levels of sIL2R. Interestingly, CCR4 expression seems to be in close association with the expression of FOXP3, a T-reg marker [22]. Further research will improve our understanding of the physiology of lymphopenia and its effect on immunosurveillance and the biology of malignancy.

Our study carries several inherent weaknesses, such as its retrospective nature and the small sample used for the analysis. Hence, there is a chance that our conclusions could have been reached by the introduction of selection bias, among others. However, we have used standard statistical techniques to perform comparisons and univariate and multivariate analyses in a non-selected population that received a uniform diagnostic and therapeutic approach.

In conclusion, our study shows that lymphopenia can be present in over one-third of patients with a diagnosis of PTCLU and is a prognostic factor for survival, independent from the PIT score. Prognostic factors are a necessary part of our risk-stratification tools as they would help clinicians set appropriate goals for their therapies. Ideal prognostic factors should be easy to implement and interpret, should be reliable, and, most important, should be validated in large retrospective or, ideally, prospective settings.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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