

Letter to the Editor

Prognostic significance of lymphocyte/monocyte count and neutrophil/lymphocyte count in peripheral T cell lymphoma



To the Editor

We read with great interest the recently published paper by Li and colleagues, that showed a lower absolute lymphocyte count/absolute monocyte count (ALC/AMC) ratio was associated with poor prognosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). In a retrospective analysis of 58 PTCL-NOS patients, ALC/AMC ratio < 2 was associated with reduced progression-free survival (PFS) and overall survival (OS); moreover, when the authors combined ALC/AMC ratio with Prognostic Index for PTCL-unspecified (PIT), 3 prognostic groups could be clearly identified [1].

PTCL are a group of rare hematological malignancies with heterogeneous morphological and biological features, but overall characterized by aggressive clinical behavior and poor prognosis [2]. Recommended first-line therapy is an anthracycline-based therapy, but complete response (CR) rate ranges from 40% to 60% and the majority of patients relapse with short PFS and OS [3]. Lenalidomide and brentuximab could be effective for relapsed cases; unfortunately in a recently published study, PTCL patients failing first-line therapy showed a dismal outcome after relapse or progression, without OS difference with respect to histology [4–7].

International prognostic index (IPI) confirmed its usefulness for PTCL since a more effective and specific prognostic model including age, performance status, LDH and bone marrow involvement was designed, called PIT [8]. However, most of the studies were retrospective and an optimal prognostic stratification has not been reached to date.

The neutrophil-lymphocyte ratio (NLR) demonstrated a prognostic role in patients with lymphoproliferative disorders, including newly diagnosed Hodgkin lymphoma (HL) and advanced stage PTCL [9,10]. In a recently published study focused on early-stage PTCL, Beltran and colleagues showed a NLR ≥ 4 vs < 4 was associated with inferior OS in a cohort of 48 patients (3-y OS was 24% and 82%, respectively; HR 6.2, 95%CI 1.9–20.9, $P = 0.003$) [11]. The aim of the authors was to find a simple and reproducible prognostic tool, that could represent a marker of systemic inflammation, permissive microenvironment and immunosuppression. However, the used cut-off value is not supported by other larger studies and the study is based on chart review, thus at least two relevant biases could be identified in the NLR calculation. In particular, PTCL patients could have received pre-phase steroid treatment that could increase absolute neutrophil count (ANC) and/or decrease lymphocyte count; furthermore, a misdiagnosed infection could also increase ANC [11].

The paper by Li and colleagues finds merit because the authors demonstrated the ALC/AMC ratio, a useful prognostic tool reflecting immune status and tumor microenvironment, could be effectively combined with PIT to better stratify PTCL patients with significantly different prognosis. The authors enrolled 58 PTCL patients and determined optimal cut-off value for ALC/AMC ratio by ROC method;

patients with leukemic disease or corticosteroid treatment were excluded [1]. ALC/AMC cut-off is consistent with the value of 2.1 that is included in the list of covariates investigated among patients registered in the T Cell Project. Remarkably, in this large prospective study, ALC/AMC ratio did not demonstrate prognostic value; 4 covariates (stage, ECOG performance status, albumin and ANC) were significantly

Table 1
Patient's characteristics.

Characteristic at diagnosis	Number of patients (%)
Age: median [range]	67 years [18–84]
Men	22/31 (70.9%)
Ann Arbor stage	3/31 (9.7%)
I	5/31 (16.2%)
II	8/31 (25.8%)
III	15/31 (48.3%)
IV	
Elevated LDH	11/31 (35.4%)
ECOG PS 0-1	23/31 (74.2%)
B symptoms	13/31 (41.9%)
Extrnodal involvement	8/31 (25.8%)
Bone marrow involvement	12/31 (38.7%)
IPI 0-2	16/31 (51.7%)
IPI 3-5	15/31 (48.3%)
PIT 0-1	11/31 (35.4%)
PIT 2-3	20/31 (64.6%)
Histological subtype	5/31 (16.2%)
AITL	1/31 (3.2%)
EATL	18/31 (58.0%)
PTCL, NOS	5/31 (16.2%)
ALCL	2/31 (6.4%)
ALK+	3/31 (9.7%)
ALK-	2/31 (6.4%)
NKTCL, nasal type	
NLR ≥ 4	10/31 (32.4%)
NLR > 6.5	8/31 (25.8%)
ANC > $6.5 \times 10^3/\text{mm}^3$	10/31 (32.4%)
ALC/AMC > 2.1	13/31 (41.9%)
First-line therapy	13/31 (41.9%)
CHOP/CHOP like	10/31 (32.4%)
CHOEP	7/31 (22.5%)
Gemcitabine-based	1/31 (3.2%)
Cyclophosphamide + prednisone	

Abbreviations: LDHlactate dehydrogenase; PSperformance status; IPIInternational Prognostic Index; PITPrognostic Index for PTCL-unspecified; AITLangoimmunoblastic T-cell lymphoma; EATLenteropathy-associated T-cell lymphoma; PTCLNOS, peripheral T-cell lymphoma, not otherwise specified; ALCLanaplastic large cell lymphoma; NLRneutrophil-lymphocyte ratio; ANCabsolute neutrophil count; ALC/AMClymphocyte-monocyte ratio; CHOPcyclophosphamide, doxorubicin, vincristine, etoposide; CHOEPCHOP plus etoposide.

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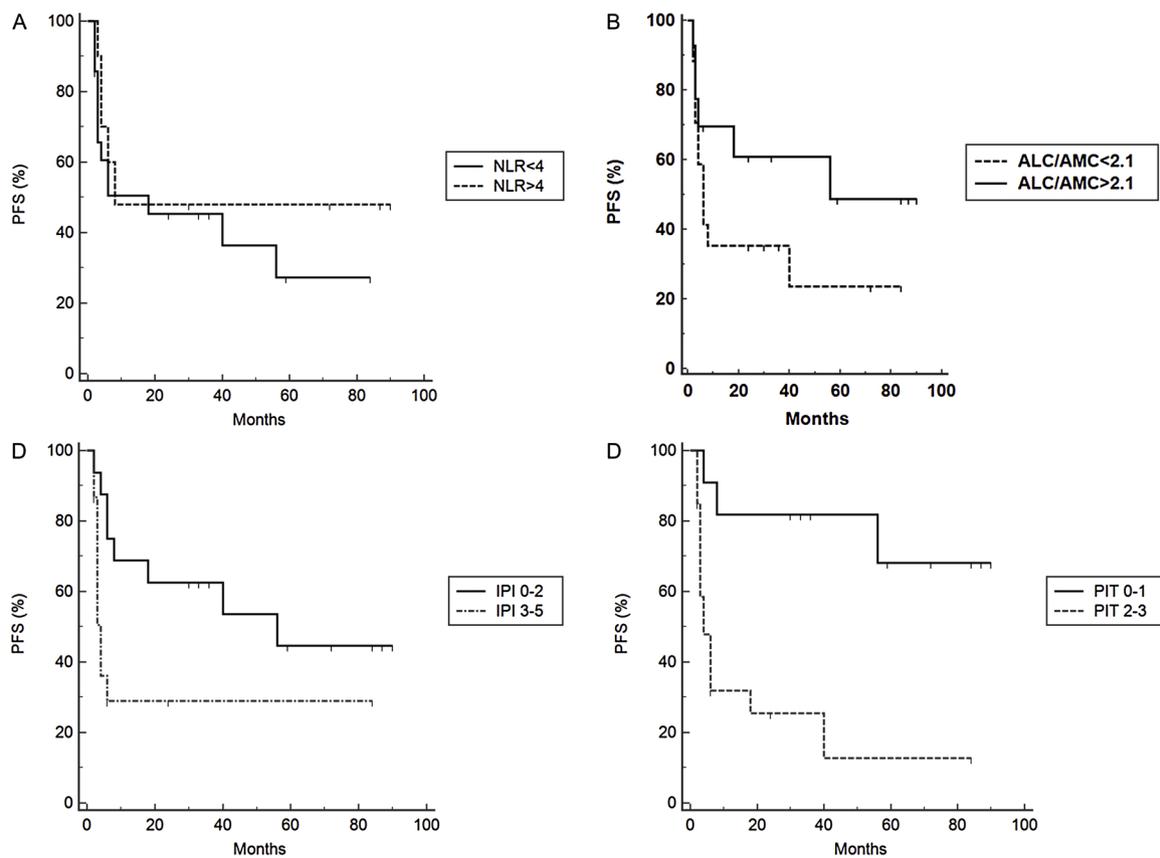


Fig. 1. Progression free survival (PFS) in PTCL patients according to neutrophil/lymphocyte ratio (NLR) (a), absolute lymphocyte count/absolute monocyte count (ALC/AMC) ratio (b), IPI (c) and PIT score (d).

associated with OS, bringing to a new prognostic model called T cell score [12].

According to this background, at our Institution, we have retrospectively investigated ALC/AMC and NLR ratio in a cohort of 31 PTCL patients diagnosed and treated between 2008 and 2017. PFS was measured from date of treatment initiation to the date of relapse, progression requiring subsequent treatment or death. Statistical analyses were performed using MedCalc software, v2.0. Survival was analyzed using the Kaplan-Meier method and the global log-rank test.

Clinical characteristics were collected through chart review and are illustrated in Table 1. All but one patients received anthracycline-based or gemcitabine-based chemotherapy with curative intent. Median age was 67 years (range 18–84), PS was > 1 in 8/31 cases (25.8%), LDH was elevated in 11/31 cases (35.4%) and bone marrow involvement was present in 12/31 cases (38.7%). IPI score was 3–5 in 15/31 cases (48.3%) and PIT score was 2–3 in 20/31 cases (64.6%). We stratified our cohort according to NLR cut-off used by Beltran and colleagues and by the International T-cell project; we also determined ALC/AMC, as previously published [12]. NLR was ≥ 4 and > 6.5 in 10 and 8 out of 31 cases, respectively; ALC/AMC was > 2.1 in 13/31 cases.

After a median follow-up of 24 months, median PFS was 8 months for the entire cohort. The 2-y PFS was 48% and 45% for patients with $\text{NLR} \geq 4$ and $\text{NLR} < 4$, respectively (HR 1.49, 95% CI 0.57–3.9, $P = \text{n.s.}$; Fig. 1a); we have achieved similar results when we have used the NLR cut-off of 6.5. The 2-y PFS for cases with $\text{ALC/AMC} > 2.1$ or < 2.1 was 58% vs 38%, respectively (HR 0.59, 95%CI 0.23–1.50, $P = \text{n.s.}$; Fig. 1b). Patients with IPI score 0–2 had increased PFS compared to IPI 3–5 (2-y PFS 62% vs 28%, HR 0.41, 95% CI 0.15–1.08, $P = 0.03$; Fig. 1c). We have performed multivariate analysis to compare the IPI and ALC/AMC; IPI score confirmed its value (HR 0.30, 95% CI 0.11–0.83, $P = 0.02$); ALC/AMC was not prognostic (HR 0.60, 95% CI 0.21–1.66, $P = \text{n.s.}$). PIT score 0–1 was associated with improved PFS

compared to PIT score 2–3 (2-y PFS 81% vs 25%, HR 0.19, 95% CI 0.07–0.49, $P = 0.001$; Fig. 1d). OS analysis showed similar results. In our cohort of PTCL patients we did not report a significant correlation between $\text{ALC/AMC} > 2.1 \times 10^3/\text{mm}^3$ and improved PFS, consistently with the results of T cell project, even if a trend could be identified. We acknowledge that the HR 0.59 could be not significant given the small sample size.

ALC/AMC and NLR could be used as biomarkers of immune function and tumor microenvironment since increased monocytes and lymphopenia could both promote tumor invasion, angiogenesis and reduced immune function, favoring tumor growth and progression. The results of our study showed a trend for better PFS with high ALC/AMC compared to low ALC/AMC (58% vs 38%, respectively); most likely the reasons for this finding could be the small sample size and the median follow-up of only 2 years. Our study has some limitations, most notably the retrospective study design and small sample size (although these were comparable to previously published experiences) and the likely heterogeneity of treatment regimen. In our opinion ALC/AMC and NLR alone could not represent a suitable marker for PTCL patients stratification because their value could be influenced by multiple variables and an optimal cut-off has not been determined to date. Our small study is far from being confirmatory, our results about ALC/AMC are in agreement with T-cell project and not in agreement with other published experiences; therefore our intention is to pay attention to the conflicting findings in this field and to recommend additional research.

ALC/AMC and NLR could provide relevant informations if included in a prognostic model together with clinical and serological variables, as it was done in the recently published T cell score and in the paper by Li and colleagues [1,12].

We suggest a promising research field could be represented by the study of permissive microenvironment, especially tumor-associated macrophages (TAM), since they could represent a more effective and

less biased tool compared to ALC/AMC value. Macrophages are characterized by remarkable plasticity; depending on the stimuli that trigger their activation, they are polarized towards form M1 (leading to anti-tumor responses) or form M2 (leading to tumor growth and progression). In our opinion and according to promising results obtained in non-hematological malignancies, future efforts should be focused on M2-TAMs, which are characterized by a protumoral phenotype. TAM demonstrated a prognostic role in multiple solid tumors and lymphoproliferative disorders, such as HL, diffuse large B-cell lymphoma (DLBCL) and multiple myeloma, even if with conflicting results [13–15]. Wang et al retrospectively reported shorter PFS and OS related to a low ALC/AMC and a high M2-TAM content in 355 DLBCL patients. These results suggest weak antitumor immunity could be an adverse prognostic factor for aggressive lymphomas, identifying high-risk patients [15].

In conclusion, we can't discard yet the ALC/AMC in comparison to T-cell score and M2 TAM as a marker to stratify PTCL patients. We suggest the optimal use of ALC/AMC should be in association with T-cell score or PIT score to better stratify PTCL patients, with the aim to investigate a novel therapeutic approach for poor risk patients in the context of a multicenter clinical trial.

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Authors' contributions

E.C. and A.F. analysed and interpreted data, performed statistical analysis and drafted the manuscript; A.S. analysed and interpreted data; M.B. contributed to data analysis and finally supervised the manuscript.

Conflict of Interest

None.

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