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The neutrophil-lymphocyte ratio is prognostic in patients with early stage aggressive peripheral T cell lymphoma

Peripheral T cell lymphoma (PTCL) is rare in the United States and Europe, accounting for about 10% of all lymphoma cases. In Latin America, PTCL accounts for about 15–20% of all lymphoma cases (Laurini *et al*, 2012). Aggressive subtypes of PTCL carry a poor prognosis with a 5-year overall survival (OS) of approximately 30%, and include

unspecified (PTCLU), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic lymphoma, among others (Vose *et al*, 2008). The International Prognostic Index (IPI) and the Prognostic Index for PTCLU (PIT) scoring systems are powerful risk-stratification tools that have been validated in patients with aggressive PTCL. The prognosis of aggressive PTCL patients is, however, heterogeneous and further refinement of prognostic tools is needed. The neutrophil-lymphocyte ratio (NLR) has been shown to be prognostic in patients with a variety of haematological malignancies (Porrata *et al*, 2010; Marcheselli *et al*, 2016; Shi *et al*, 2017). In a previous study, we showed that the NLR was prognostic in patients with advanced stage PTCLU (Beltran *et al*, 2016). Early stage disease has been associated with a better survival than patients with advanced stage disease. The aim of this study was to evaluate whether the NLR is a prognostic factor in patients with early stage aggressive PTCL.

We included consecutive patients with a pathological diagnosis of aggressive PTCL who were diagnosed and treated at our institution between 2001 and 2016. We excluded cases with stage 3 or 4 disease. Institutional Review Board approval was obtained prior to research. Pathological samples were reviewed by two haematopathologists to confirm and/or reclassify the diagnosis according to the most recent World Health Organization classification criteria for T cell lymphomas. All patients received standard anthracycline-based chemotherapy with or without radiotherapy with a curative intent. Pertinent clinicopathological data were collected through chart review, and are presented using descriptive statistics. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and dichotomized as NLR≥4 and NLR < 4. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox models were fitted to evaluate prognostic factors for OS. Outcomes are reported as hazard ratios (HRs) with 95% confidence interval (CIs). $P < 0{\cdot}05$ were considered statistically significant. Calculations and graphs were obtained using STATA (StataCorp, College Station, TX, USA).

Forty-eight patients with a diagnosis of early stage PTCL were included in this analysis. Histologically, 40 patients (83%) were PTCL, not otherwise specified, 7 (15%) were anaplastic lymphoma kinase-negative anaplastic large cell lymphoma and 1 (2%) was enteropathy-associated T cell lymphoma. The median age at diagnosis was 60 years (range 18–83 years) with a slight male predominance (52%). Clinically, 49% of patients were 60 years of age or older, 34% presented with Eastern Cooperative Oncology Group

Table I. Patients' characteristics based on the neutrophil-lymphocyte ratio.

Characteristic	Total (n = 48)	NLR < 4 (n = 35)	NLR ≥ 4 (n = 13)	P-value
Age >60 years	23 (49%)	18 (53%)	5 (38%)	0·52
Male sex	25 (52%)	15 (43%)	10 (77%)	0·05
ECOG performance status				
0	15 (33%)	15 (45%)	0 (0%)	0·01
1	19 (42%)	14 (42%)	5 (42%)	
2	8 (18%)	3 (9%)	5 (42%)	
>2	3 (7%)	1 (3%)	2 (17%)	
Elevated LDH level	14 (36%)	9 (31%)	5 (50%)	0·45
Extranodal involvement	31 (65%)	23 (66%)	8 (62%)	1·00
Head and neck	17 (55%)	13 (57%)	4 (50%)	1·00
Gastrointestinal tract	6 (19%)	4 (17%)	2 (25%)	0·63
Soft tissue	4 (13%)	3 (13%)	1 (13%)	1·00
Other sites*	4 (13%)	3 (13%)	1 (13%)	1·00
Stage 2 disease	21 (44%)	13 (37%)	8 (62%)	0·19
Histological subtype				
PTCL, NOS	40 (83%)	29 (83%)	11 (85%)	0·83
ALK-negative ALCL	7 (15%)	5 (14%)	2 (15%)	
EATCL	1 (2%)	1 (3%)	0 (0%)	
High/high-intermediate IPI	13 (30%)	6 (19%)	7 (54%)	0·03
High/high-intermediate PIT	13 (34%)	7 (27%)	6 (50%)	0·15
Response to therapy				
Complete response	25 (52%)	21 (74%)	4 (29%)	0·01
Partial response	6 (19%)	3 (13%)	3 (23%)	
No response	9 (29%)	3 (13%)	6 (43%)	

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EATCL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PIT, Prognostic Index for Peripheral T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified.

*Other sites include lung (n = 1), spleen (n = 1), breast tissue (n = 1) and uterine cervix (n = 1).

performance status >1, 36% with elevated serum lactate dehydrogenase (LDH) level, and 65% with ≥1 extranodal site of involvement. Twenty-one patients (44%) had stage II and 27 (56%) had stage I disease. No patient had bone marrow involvement. Based on standard risk-stratification tools, 30% of patients presented with high/high-intermediate IPI score and 34% with high/high-intermediate PIT score. Based on the NLR, 13 patients (27%) had a NLR ≥ 4. There were no differences in age, sex, serum LDH levels, extranodal involvement, stage or histological subtype between the NLR ≥ 4 and NLR < 4 groups (Table I). Patients with NLR ≥ 4 had a worse performance status ($P = 0{\cdot}01$), as well as worse response to therapy ($P = 0{\cdot}01$). The median follow-up for the entire group was 36 months. The median OS was not reached and the 3-year OS rate was 67% (95% CI 50–80%). Patients with NLR ≥ 4 had a higher risk of death (HR 9·9, 95% CI 3·2–30·1; $P < 0{\cdot}001$). The 3-year OS for patients with NLR ≥4 was 24% (95% CI 4–53%) compared to 82% (95% CI 60–92%) in patients with NLR < 4 (Fig 1A). High/high-intermediate IPI score was also associated with a worse outcome (HR 4·9, 95% CI 1·7–14·2; $P = 0{\cdot}001$; Fig 1B), as well as high/high-intermediate PIT score (HR 3·9, 95% CI 1·2–12·7; $P = 0{\cdot}018$; Fig 1C). In a multivariate analysis adjusting for IPI and PIT scores, NLR ≥ 4 was the only independent factor associated with a worse survival (HR 6·2, 95% CI 1·9–20·9; $P = 0{\cdot}003$). In a stratified analysis, NLR ≥ 4 was an adverse prognostic factor in patients with low/low-intermediate IPI (HR 8·33, 95% CI 1·84–37·7, $P = 0{\cdot}006$) and high/high-intermediate IPI score (HR 9·72, 95% CI 1·10–85·9, $P = 0{\cdot}04$). NLR ≥ 4 was also an adverse prognostic factor in patients with low/low-intermediate PIT (HR 5·83, 95% CI 1·29–26·4, $P = 0{\cdot}02$) and high/high-intermediate IPI score (HR 10·1, 95% CI 1·09–94·1, $P = 0{\cdot}04$).

Based on the results of our study, the NLR appears to be a novel and easy-to-use prognostic factor for worse response and shorter OS in patients with previously untreated early stage, aggressive PTCL. Biologically, the NLR can serve as a reflection of two separate but interrelated underlying processes in lymphomas. Specifically, the absolute neutrophil count might serve as a marker of systemic inflammation, which can provide a permissive environment for the development of lymphoma (Carbone *et al*, 2014). On the other hand, the absolute lymphocyte count might be reflective of immunosuppression, which has also been associated not only with development of lymphoma but also with a worse outcome in a number of solid and haematological malignancies (Castillo *et al*, 2010; Wei *et al*, 2015). The biological interaction of these factors might have clinical relevance and provide prognostic information additional to well-established prognostic tools. Our stratified analysis showed that the NLR could add prognostic value to the IPI and the PIT scores. Importantly, patients with early stage aggressive PTCL and NLR ≥ 4 have a dismal prognosis of less than 25% at 3 years. By defining a group of patients with poor prognosis, we look towards developing novel approaches in those patients, and a few questions arise: Should we offer treatment options beyond or distinct from anthracycline-based therapy, with or without radiotherapy? Should we pursue multicentre clinical trials with novel agents specifically in those patients? Although these questions remain unanswered for now, we believe that our findings support the need for validation of the NLR in larger retrospective or prospective studies in patients with PTCL.

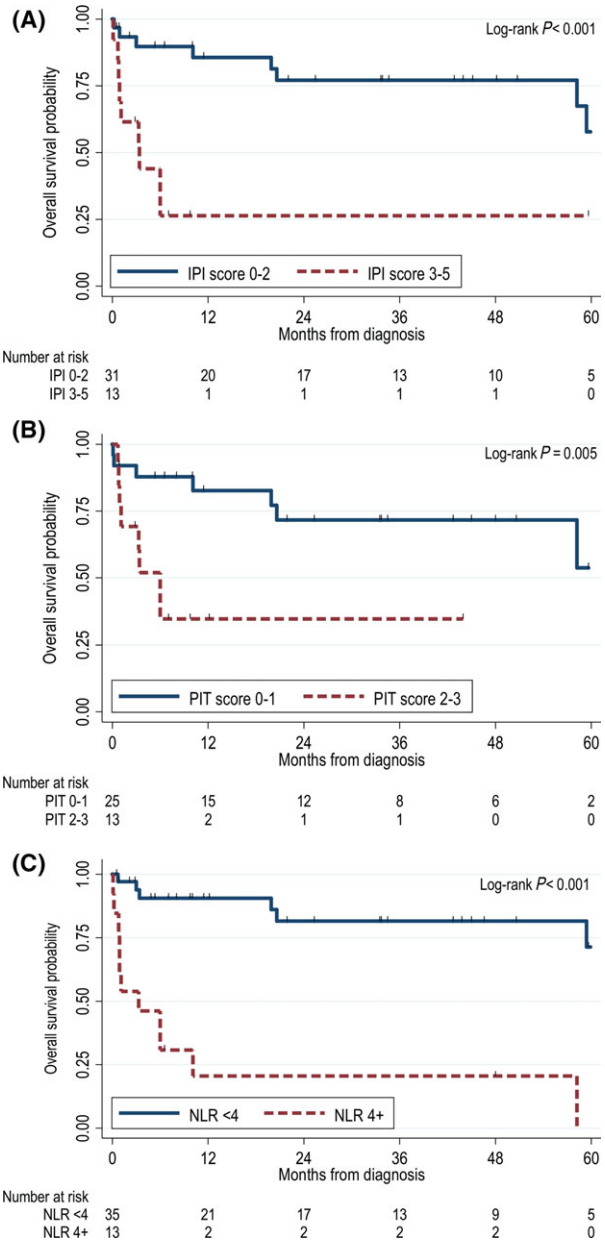

Fig 1. Overall survival curves in 48 patients with PTCL according to (A) neutrophil-lymphocyte ratio (NLR), (B) International Prognostic Index (IPI) and (C) Prognostic Index for Peripheral T-cell lymphoma (PIT). [Colour figure can be viewed at wileyonlinelibrary.com]

Disclosures

The authors have no conflict of interest to disclose.

Authorship

BEB and JJC designed the study and wrote the manuscript. BEB, DC, JC, EC and AG carried out the research. All the authors reviewed and approve the manuscript.

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Cord gas parameters in infants born to women with sickle cell disease: a retrospective matched cohort study

Women with sickle cell disease (SCD) often experience adverse fetal events (Villers *et al*, 2008), probably placentally-mediated (Rathod *et al*, 2007). Given the placental role in fetal gas-exchange, umbilical cord blood gas (UCBG) analysis provides insight into intrapartum placental function and fetal acid-base status (American College of Obstetricians and Gynecologists [ACOG] Committee on Obstetric Practice 2006), enabling detection of metabolic acidosis, with established links to adverse outcomes (Armstrong & Stenson, 2007) but has not been studied in SCD. We aimed to determine whether UCBGs in infants of SCD-affected women (cases) differ from infants of non-affected women (controls).

This was a retrospective cohort study of SCD-affected pregnant women attending the Special Pregnancy Program at Mount Sinai Hospital (MSH), Canada (January 2004–December 2015). Inclusion criteria comprised SCD-diagnosis