ORIGINAL ARTICLE

Prognostic Impact of Inflammatory Biomarkers in Diffuse Large B-Cell Lymphoma: Analysis of a Cohort of 76 Patients

Impact pronostique des biomarqueurs inflammatoires dans le lymphome B diffus à grandes cellules : Analyse d'une cohorte de 76 patients

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Abstract

Introduction: Inflammation plays a key role in the progression of diffuse large B-cell lymphoma (DLBCL). Biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been associated with prognosis in various malignancies. This study evaluates their prognostic impact in DLBCL.
Methods: We retrospectively analyzed 76 patients diagnosed with DLBCL. NLR, PLR, and SII were calculated before treatment. Associations with clinical and biological parameters were assessed using univariate analysis (Chi-square test). A multivariate analysis was performed using Cox regression to determine independent prognostic factors.
Results: Elevated PLR was significantly associated with higher performance status (PS) and increased lactate dehydrogenase (LDH) levels, which are known poor prognostic factors in DLBCL. However, in multivariate Cox regression analysis, PLR was not identified as an independent prognostic factor for survival. NLR and SII showed trends toward similar associations but did not reach statistical significance.
Conclusion: While PLR correlates with key clinical and biological indicators of disease severity, it does not appear to be an independent prognostic factor in DLBCL. Further studies with larger cohorts are needed to clarify its prognostic value.

Key words : Diffuse large B-cell lymphoma, Prognosis, Inflammation, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Systemic immune-inflammation index

Résumé

Introduction: L'inflammation joue un rôle clé dans la progression du lymphome B diffus à grandes cellules (LBDGC). Des biomarqueurs tels que le rapport neutrophiles/lymphocytes (NLR), le rapport plaquettes/lymphocytes (PLR) et l'indice systémique d'inflammation immunitaire (SII) ont été associés au pronostic de diverses tumeurs malignes. Cette étude évalue leur impact pronostique dans le LBDGC.
Méthodes : Nous avons analysé rétrospectivement 76 patients atteints de LBDGC. Les valeurs de NLR, PLR et SII ont été calculées avant le traitement. Les associations avec les paramètres cliniques et biologiques ont été évaluées en analyse univariée (test du Khi-2). Une analyse multivariée par régression de Cox a été réalisée pour identifier les facteurs pronostiques indépendants.
Résultats : Un PLR élevé était significativement associé à un indice de performance élevé, et une augmentation du taux de lactate déshydrogénase (LDH) qui sont des facteurs de mauvais pronostic connus dans le LBDGC. Cependant, l'analyse multivariée par régression de Cox n'a pas identifié le PLR comme un facteur pronostique indépendant de survie. Le NLR et le SII ont montré des tendances similaires, sans atteindre la significativité statistique.
Conclusion : Bien que le PLR soit corrélé à des indicateurs cliniques et biologiques de gravité de la maladie, il ne semble pas constituer un facteur pronostique indépendant dans le LBDGC. Des études supplémentaires sur des cohortes plus larges sont nécessaires pour préciser sa valeur pronostique.

Mots-clés : Lymphome diffus à grandes cellules B ; Pronostic ; Inflammation ; Rapport neutrophiles/lymphocytes ; Rapport plaquettes/lymphocytes ; Indice d'immuno-inflammation systémique.

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LA TUNISIE MEDICALE-2026; Vol 104 (08): 940-944 DOI: 10.62438/tunismed.v104i08.5946

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What is known ?

• Inflammation plays a key role in the progression of diffuse large B-cell lymphoma (DLBCL).

• Biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been associated with prognosis in various malignancies.

• Their prognostic significance in DLBCL remains unclear.

What this article adds ?

• This study shows that an elevated PLR is associated with poor prognostic factors such as high performance status and increased LDH levels.

• However, multivariate Cox regression analysis indicates that PLR is not an independent prognostic factor for survival.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), with an increasing incidence with age. Its prognosis depends on several factors, including the patient's performance status, lactate dehydrogenase (LDH) level, and disease stage, summarized in the age-adjusted International Prognostic Index (IPIaa). Although several new prognostic factors have been proposed, their additional value over IPIaa remains to be demonstrated.
In this context, inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been studied for their prognostic impact in various tumor types. However, their relevance in DLBCL remains insufficiently explored.
In this study, we aimed to describe the epidemiological, clinical, and biological characteristics of patients with DLBCL and analyze the prognostic impact of NLR and PLR on treatment response, overall survival (OS), progression-free survival (PFS), and relapse-free survival (RFS).

Methods

Study Type and Setting

This is a longitudinal and analytical study including 76 patients with DLBCL followed at the clinical hematology department of Fattouma Bourguiba University Hospital in Monastir over a period of 21 years (2003-2024).

Inclusion Criteria

Patients included in the study had to meet the following criteria:

- Age ≥ 18 years.
- Confirmed diagnosis of DLBCL.
- Treatment according to the national LNH2013 protocol (table 1).

Data Collection

Data were collected from medical records using pre-established forms. Diagnosis was confirmed by lymph node or extranodal biopsy and analyzed according to the Hans algorithm. An extension workup included bone marrow biopsy (BMB) and imaging (CT scan and, if available, PET-CT).

Treatment and Assessment

Patients were classified into five therapeutic groups according to the IPIaa (table 1) and treated with a regimen based on Rituximab, prednisone, cyclophosphamide, vincristine, and doxorubicin (RCHOP) according to the National protocol (LNH-2013) (table 2).

Table 1. Age-adjusted international prognostic index

aaIPI depends on 3factors : • **PS : 0-1 versus 3-4** • **LDH level : normal versus high** • **Stage : I-II versus III-IV**	**Risk**
0 factor	low
1 factor	Low-intermediate
2 factors	intermediate
3 factors	high

PS =performance status, **LDH** = lactate dehydrogenase

Table 2. The National Protocol (LNH-2013)

	18-60 years	**61-75 years**	**>75 years**
aaIPI = 0	Groupe 1 : 6 RCHOP21		Groupe 4 :
aaIPI =1	Groupe 2A :	Groupe 3 :	6 mini-RCHOP21
	8 RCHOP21	8 RCHOP 21	
aaIPI =2-3	Groupe 2B :		
	4 RCHOP14 + autologous stem cell transplantation		

aaIPI= age-adjusted International Prognostic Index, RCHOP= Rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone, 21,14= number of days seperating two cycles of chemotherapy

Disease assessment was performed at the midpoint and at the end of treatment.

Statistical Analysis

All analyses were performed using IBM SPSS version 21.
NLR was calculated by dividing the absolute neutrophil count ($\times 10^9$/L) by the absolute lymphocyte count ($\times 10^9$/L) (normal value ranges between 2.5 and 5).
PLR was calculated by dividing the platelet count ($\times 10^9$/L) by the absolute lymphocyte count ($\times 10^9$/L) (normal value ranges between 150 and 170).
SII was calculated as platelet count × neutrophil count / lymphocyte count (all in $\times 10^9$/L) (normal value ranges between 400 and 1000).
ROC curves were used to determine the optimal cut-off values for NLR, PLR, and SII, as well as to measure the area under the curve (AUC). Accordingly, biomarker values exceeding the cut-off thresholds were classified as high, whereas those at or below the thresholds were classified as normal (Low NLR, low PLR and low SII).

The impact of prognostic factors on overall survival (OS), progression-free survival (PFS), and relapse-free survival (RFS) was assessed using Kaplan–Meier curves and compared with the log-rank test. The Chi-square test was used to evaluate the correlation between NLR, PLR, and SII ratios and established prognostic factors.
For the multivariate analysis, variables with a p-value ≤ 0.25 in univariate analysis were included in a binary logistic regression model. Variables with a statistically significant association at a 5% error risk were retained.

Results

Epidemiological and Biological Characteristics

The median age of patients was 55 years [18-86], with a female predominance and a sex ratio of 0.76. Impaired performance status (PS ≥2) was observed in 23.7% of patients. Anemia was frequent, affecting 52% of cases, and elevated LDH was found in 50% of patients. Advanced stage was observed in 47.4% of patients (77.6% of them had a stage IV). The patients were devised into 5 groups according to the aaIPI (fig.1).

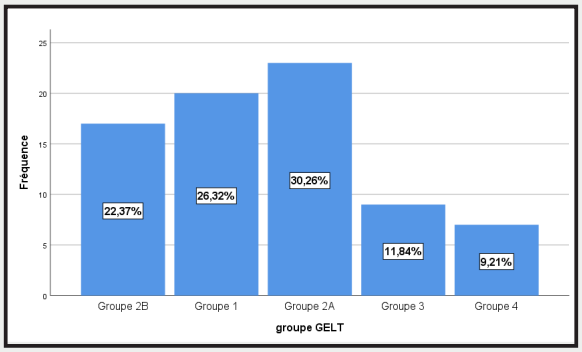


Figure 1. Distribution of patients according to the therapeutic groups of the 2013 NHL. protocol

Regarding inflammatory biomarkers, the median NLR was 2.88 (cut-off: 3.76, AUC: 0.57), PLR was 159.47 (cut-off: 218.23, AUC: 0.65), and SII was 716.23 (cut-off: 1054.7, AUC: 0.6) (Fig.2).

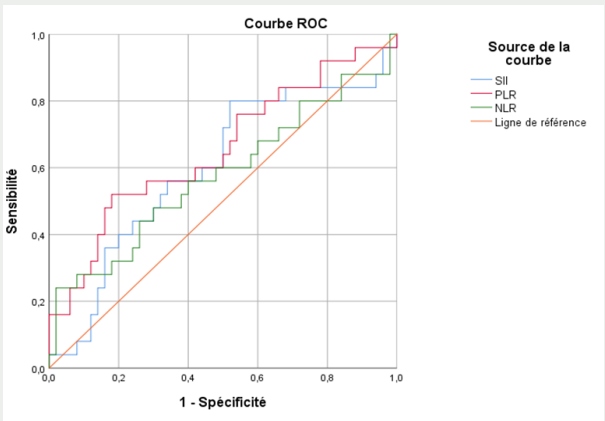


Figure 2. ROC Curve and Area Under the Curve

Survival and Prognostic Factors

The 5-year overall survival (OS) rate was 74.4%, while progression-free survival (PFS) was 83%, and relapse-free survival (RFS) was 96.9% (Fig.2).

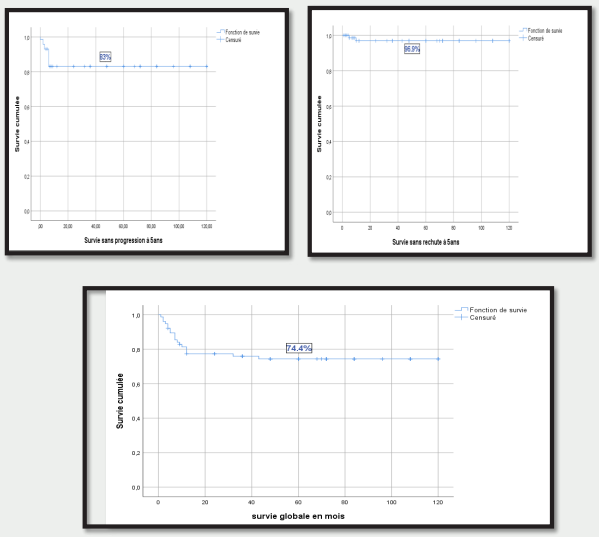


Figure2. The 5-year overall survival(C), progression-free survival(A) and relapse-free survival (B)

Univariate study

Kaplan–Meier analysis showed that several factors had a significant adverse impact on OS. Patients with a high PLR had markedly shorter survival compared to those with a low PLR (p = 0.011). Advanced Ann Arbor stage was associated with reduced survival (p = 0.002), as was elevated LDH level (p = 0.021) and poor performance status (PS ≥ 2) (p < 0.001). The aaIPI demonstrated a clear gradient in survival, with high-risk patients showing the poorest outcomes (p < 0.001). Moreover, failure to achieve complete remission at interim evaluation was strongly associated with inferior survival (p = 0.002). In contrast, SII, histological subtype, sex, and NLR did not significantly influence survival in this cohort (Table 3).

We then assessed the impact of these same factors on the occurrence of disease progression or relapse and found no statistically significant association. The impact of PLR on OS is shown in the figure below (Fig.3).

The correlation between the newly evaluated prognostic factors (SII, NLR, and PLR) and established prognostic factors (Chi-square test) showed that a high PLR was moderately correlated with elevated LDH levels (r = 0.257, p = 0.027) and poor performance status (r = 0.287, p = 0.015), but was not correlated with early response at interim evaluation (p = 0.43), histopathological subtype (p = 0.68), or Ann Arbor stage (p = 0.052). NLR was correlated only with LDH levels (r = 0.226, p = 0.024). Elevated SII was not correlated with any of the established prognostic factors.

Table 3. Impact of Prognostic Factors on Overall Survival: Univariate Study

Factor	Category	N (%)	Mean survival (months)	p (Log-Rank)
High PLR	No	49 (66.2%)	101.1	0.011
	Yes	25 (33.8%)	51.6	
High SII	No	54 (73.0%)	92.1	0.747
	Yes	20 (27.0%)	79.8	
Ann Arbor stage	Localized	40 (53.3%)	107.4	0.002
	Advanced	35 (46.7%)	73.1	
Histological type	Germinal center (GC)	14 (18.4%)	96.4	0.846
	Non–germinal center (non-GC)	28 (36.8%)	83.7	
	Not specified	34 (44.7%)	89.6	
LDH (normal / elevated)	Normal	38 (50.0%)	105.1	0.021
	Elevated	38 (50.0%)	78.9	
Performance status (PS)	PS = 1	58 (79.5%)	101.3	< 0.001
	PS ≥ 2	15 (20.5%)	43.3	
Patient sex	Male	33 (43.4%)	85.3	0.341
	Female	43 (56.6%)	96.7	
aaIPI	Low risk	21 (30.4%)	110.6	< 0.001
	Low–intermediate risk	25 (36.2%)	107.2	
	Intermediate–high risk	15 (21.7%)	66.9	
	High risk	8 (11.6%)	22.0	
Status at interim assessment	CR	43 (66.2%)	109.9	0.002
	No CR	22 (33.8%)	53.7	
High NLR	No	51 (68.9%)	92.7	0.675
	Yes	23 (31.1%)	87.7	

CR :complete remission, **aaIPI** : age-adjusted international prognostic index, **NLR** : Inflammation, Neutrophil-to-lymphocyte ratio, **PLR** : Platelet-to-lymphocyte ratio, **SII** :Systemic immune-inflammation index.

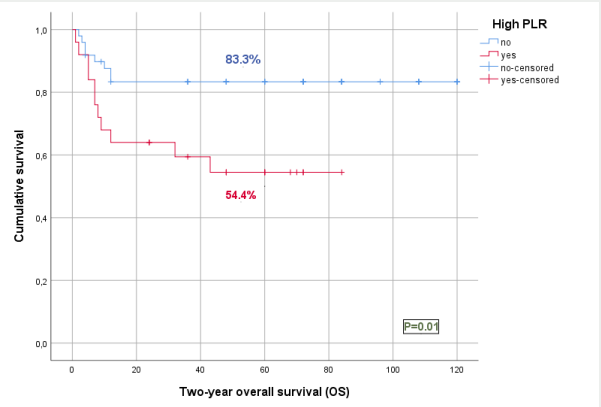


Figure 3. Impact of the Platelet/lymphocyte ratio on the overal survival

Multivariate Analysis

This study was conducted using the Cox regression model (stepwise backward Wald method) and showed that none of the prognostic factors had an independent influence on overall survival.

Discussion

NLR

In recent years, several studies (1–5) have explored the role of the neutrophil-to-lymphocyte ratio (NLR) as a prognostic indicator in different types of cancers. This ratio is recognized as a factor influencing the evolution of many malignancies. Our results show that patients with a low NLR have significantly better survival rates. These results align with those of other studies, such as KETM (6).

Neutrophils, as inflammatory cells, secrete several angiogenic factors (7), such as VEGF, IL-8, and matrix metalloproteinases, which promote tumor invasion and metastasis formation. Their activity plays a key role in tumor progression and stimulates the proliferation of cancer cells (8).

Lymphocytes, essential for the immune response, can inhibit the growth of tumor cells. A decrease in lymphocyte count leads to increased release of immune mediators, thereby promoting tumor progression (9,10). An increase in the NLR indicates either an elevation in neutrophil numbers or a decrease in lymphocytes. This weakens the immune response and makes the body less able to fight the tumor, which is often associated with poor prognosis.

Some studies have confirmed the prognostic impact of NLR in DLBCL (11), but others, such as this one, found no significant correlation between this ratio and disease progression (12,13).

PLR

Zhao et al. and other researchers have highlighted the significance of the platelet-to-lymphocyte ratio (PLR) in the evaluation of borderline ovarian tumors and its prognostic role in various cancers (14). Our results indicate that a high PLR is associated with a lower survival rate, suggesting a less favorable clinical course. Platelets, by participating in systemic inflammation, contribute to tumor progression (15). The elevation in PLR may result from increased platelet numbers due to immune dysfunction or decreased lymphocyte numbers. This situation favors disease progression and is linked to poor prognosis.

A 2019 meta-analysis, including 49 studies, showed that PLR is associated with several known prognostic factors such as B symptoms, high LDH levels, advanced stage, and PS ≥2 (16). In our study, we confirmed the prognostic impact of PLR on OS in univariate analysis and demonstrated its correlation with LDH levels (p=0.0257) and PS (p=0.287). However, in multivariate analysis, this factor was not identified as an independent factor, unlike a study of 175 patients by Yan Li et al., where PLR was found to be an independent prognostic factor. This discrepancy may be attributed to the smaller sample size in our study.

SII

An elevated systemic immune-inflammation index (SII) is recognized as a poor prognostic factor in several solid cancers, such as pancreatic (17), breast (18), lung (19), and gastrointestinal cancers (20). The first study conducted in 2021 on 224 patients with DLBCL found that high SII is a detrimental factor, correlated with elevated LDH levels, high PS, and advanced stage, adversely affecting OS and PFS (21). These results were confirmed by a meta-analysis published in 2023 (22). According to our data, SII was only correlated with PS (p=0.050) and did not affect the survival outcomes studied.

The limitations of our study are related to its retrospective nature and the relatively small sample size, which may limit statistical power. Larger prospective studies are necessary to better assess the impact of these inflammatory biomarkers and their potential contribution to the prognostic stratification of DLBCL.

Conclusion

Our results confirm the importance of stage and LDH as major prognostic factors in DLBCL. Although PLR seems to have an interesting discriminative value, it does not constitute an independent factor. Further studies on larger cohorts are needed to validate the contribution of inflammatory biomarkers in the prognostic stratification of DLBCL.

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