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Original Article

Absolute Monocyte and Platelet Counts May Provide Additional Prognostic Information in Primary Gastric Diffuse Large B-cell Lymphoma Patients Treated with Rituximab and CHOP

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Abstract

Introduction: Primary gastric diffuse large B cell lymphoma (PG-DLBCL) is the most common histological subtype of primary gastric lymphoma. The standard of care of PG-DLBCL patients is the combination rituximab-based immunochemotherapy (R-CHOP). Recently, different host-related factors have been shown to have significant prognostic significance in non-Hodgkin lymphoma. However, data regarding their prognostic contribution to PG-DLBCL are limited.

Aim: To assess the prognostic impact of a panel of simple, cost-effective laboratory variables which are easy to apply in routine laboratory use for R-CHOP-treated PG-DLBCL patients in an attempt to identify those among them that are high-risk category.

Materials and methods: We retrospectively assessed the possible prognostic impact of different laboratory markers in 42 R-CHOP treated PG-DLBCL patients treated between 2004 and 2014 and followed at a single institution.

Results: The estimated 5-year overall (OS) and progression-free survival (PFS) of the whole group were 80.9% and 78%, respectively. The absolute monocyte and platelet counts in univariate analysis predicted PFS and OS when analyzed as continuous and dichotomized variables. On multivariate analysis performed with factors included in the stage-modified International Prognostic Index (m-IPI), the absolute monocyte and platelet counts remained independent predictors of PFS and OS. Therefore, the absolute monocyte and platelet counts were combined to generate a prognostic index that identified patients with an especially poor overall survival.

Conclusions: This prognostic index was independent of the m-IPI and could provide additional prognostic information for better stratification of these patients.

Keywords

cells, hematologic malignancy, immunotherapy, prognosis

INTRODUCTION

Primary gastrointestinal involvement is one of the most common extranodal presentations in non-Hodgkin lymphoma (NHL), accounting for 4–20% of all NHL cases.[1,2] The most commonly affected site of the gastrointestinal tract is the stomach, followed by the small and the large intestines.[3] Primary gastric lymphoma is accounting for 5% of primary gastric malignancies and the most common histological subtype is diffuse large Bcell lymphoma (PG-DLBCL).[4] PG-DLBCL has been treated with various modalities, including surgery, chemotherapy and radiotherapy alone or in combination with other modalities.[5-7] Presently, the combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) is the standard treatment for PG-DLBCL patients.[8,9]

However, with improved outcomes attributed to the rituximab addition, the identification of a high-risk patients' subset with an anticipated 5-year survival of less than 50% remains a challenge. Gene-expression profiling, immunohistochemistry-based detection of prognostic biomarkers and early interim analysis with positron emission tomography following the initiation of immunochemotherapy have all been explored as predictors that may identify high-risk patients.[10-16] Although promising, many of these methods are costly, difficult to obtain, and not easily interpreted. Therefore, it's worth it to identify clinically relevant prognostic factors that are inexpensive, widely available, and easily interpreted by clinicians involved in the PG-DLBCL patients' care.

Recently, a number of routine laboratory parameters such as serum albumin (SA), serum β2-microglobulin (B2M), hemoglobin level (Hb), absolute neutrophil (ANC), lymphocyte (ALC), monocyte (AMC) and platelet counts (PC) etc. were proposed to have prognostic impact in DLBCL patients.[10,17-20] The clinical utility of these markers was investigated in individual studies; however, the data regarding their prognostic impact in PG-DLBCL patients are still limited.

AIM

The purpose of the study was to assess the possible prognostic impact of a panel of simple, cost-effective and applicable for routine clinical use laboratory variables in R-CHOP-treated PG-DLBCL patients in an attempt to identify the high-risk category.

PATIENTS AND METHODS

The electronic database of the Specialized Hospital for Active Treatment of Hematological Diseases – Sofia, Bulgaria was searched for all patients diagnosed with PG-DLBCL between 2004 and 2014 and treated with a combination immunochemotherapy. Forty-two cases were identified. All PG-DLBCL patients underwent esophagogastroduodenoscopy and biopsy samples were obtained. Diagnosis was defined according to the criteria outlined in the WHO classification.[21] The immunophenotype was determined by automated immunohistochemistry (BondMax, Leica Biosystems) and a panel of monoclonal antibodies against CD20, CD5, CD10, bcl-6, MUM1/IRF4, bcl-2, and Ki-67 (Leica Biosystems) was used in all cases.

Whole-body computed tomography (CT) scanning and trephine biopsy were included as lymphoma staging procedures. The stage at presentation was assessed according to the Lugano staging system, and the localized and advanced diseases were defined as stage I-II_1 and stages II_2-IV, respectively.[22] The prognostic stratification was performed according to stage-modified International Prognostic Index (m-IPI) that included Lugano stage ≥II_2, age >60 years, elevated serum lactate dehydrogenase (LDH), performance status (PS) ≥2 and ≥1 extranodal site involvement (excluding stomach).

All patients were subjected to 6-8 curative cycles of R-CHOP regimen (day 1: rituximab 375 mg/m^2, cyclosphosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 and days 1-5: prednisone 40 mg/m^2), and each cycle was repeated every 3 weeks. After completion of therapy, evaluation of the treatment response was performed by gastroscopy with biopsy and CT of the thorax and abdomen. Response was defined according to the criteria of the International Harmonization Project.[23]

Laboratory levels of SA, Hb, LDH, B2M, ANC, AMC, ALC and PC were recorded at time of diagnosis.

Statistical analysis

A receiver operating characteristic (ROC) curve analysis was used to illustrate in our data set the best cut-off values of SA, B2M, Hb, ANC, AMC, ALC and PC to predict progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier method.[24] PFS was calculated from the date of diagnosis to the date of disease progression, death or last follow-up. OS was calculated from the date of diagnosis to the date of death or last follow-up. The log-rank test was used to compare subgroups in the univariate analysis of survival. Multivariate analysis of factors related to survival was performed using the Cox's proportional hazards regression method considering variables that were statistically significant according to the univariate analysis.[25] The effect size was reported as a hazard ratio (HR) with the associated 95% confidence interval (95% CI). Comparisons were performed using Fisher's exact test for binary variables and Kruskal-Wallis nonparametric test for continuous variables. P values <0.05 were considered statistically significant. All data were analyzed using SPSS, version 15 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients' characteristics

The characteristics of 42 PG-DLBCL patients included in the present study are shown in **Table 1**. The patients' median age was 56.7 years (range, 19.1–76.4 years). Overall response was observed in 78.6 % patients - complete and partial responses were achieved in 76.2% and 2.4%, respectively. Six patients received salvage therapy whereas two other patients with progressive disease underwent autologous stem cell transplantation. One patient refused further therapy. At the time of analysis, 10 patients progressed and 8 of them died. Median follow-up was 36 months for the entire cohort (range, 2.4–135 months) and 49 months for censored patients (range, 13–132 months). The 5-year PFS and OS for the entire cohort were estimated as 78.0% and 80.9%, respectively.

Univariate analysis of the main prognostic variables

Univariate analysis (Cox regression) of the main prognostic factors for OS and PFS was performed. The HR and the confidence interval (95% CI), and statistical significance were determined for each continuous variable **(Table 2)**. As continuous variables, SA, B2M, ANC, AMC, and PC had a significant impact on OS and PFS **(Table 2)**.

Using data from the entire cohort, we select the most discriminative cut-off values for the SA, B2M, ANC, ALC, AMC, Hb, and PC to predict survival outcome by ROC curve analysis **(Tables 3, 4)**.

Prognostic Significance of Monocyte Counts

The median AMC at diagnosis was 0.518×10^9/L (range, 0.09 – 1.24×10^9/L) and 4 patients had a count above the upper normal level (0.8×10^9/L). The median AMC was significantly lower in m-IPI risk groups with scores 0-1 compared to risk groups with scores ≥2 (0.43×10^9/L vs. 0.519×10^9/L, p=0.046). As a continuous variable, the AMC was significantly associated with shorter survival endpoints **(Table 2)**. The most discriminative AMC cut-off value on the ROC curve was >0.518×10^9/L predicting for OS **(Table 3)** and PFS **(Table 4)**, respectively.

AMC values above the cut-off value of 0.518×10^9/L were observed in 42.9%. No association was established between AMC and other characteristics **(Table 5)**. After dichotomization by the most discriminative cut-off value, AMC>0.518×10^9/L predicted for shorter OS and PFS **(Figs 1A, 1B)**. The 5-year OS was 95.7% in patients with AMC≤0.518×10^9/L compared to 61.1% in those with higher AMC (p=0.004), whereas the 5-year PFS was 91.7% in patients with AMC≤0.518×10^9/L compared to 55.6% in those with higher counts (p=0.004).

Table 1. Patients' characteristics (n = 42)

Characteristic	No	%
Age (years)		
>60	16	38.1
≤60	26	61.9
Sex		
Male	23	54.8
Lugano stage		
Early (I-II_1)	13	30.9
Advanced (II_2-IV)	29	69.1
ECOG PS		
≥2	13	30.9
<2	29	69.1
Lactate dehydrogenase		
Elevated	15	35.7
Normal	27	64.3
Serum albumin		
≥35 g/L	26	61.9
<35 g/L	16	38.1
Beta-2-microglobulin		
Elevated	29	69.1
Normal	13	30.9
Absolute neutrophil count		
<2.1×10^9/L	3	7.1
≥2.1×10^9/L	39	92.9
Absolute lymphocyte count		
<1.1×10^9/L	4	9.5
≥1.1×10^9/L	38	90.5
Absolute monocyte count		
≤0.8×10^9/L	38	90.5
>0.8×10^9/L	4	9.5
Hemoglobin level		
<120 g/L	18	42.9
≥120 g/L	24	57.1
Platelet count		
≤440×10^9/L	31	73.8
>440×10^9/L	11	26.2
Bone marrow involvement*		
positive	1	2.6
negative	38	97.4
m-IPI[a]		
0-1	14	33.3
≥2	28	66.7
	Median (range)	
Age	56.7 (19.1–76.4)	
Serum albumin (g/L)	39.1 (22.4-49.4)	
Beta-2 microglobulin (mg/L)	2.95 (1.2-13.9)	
Absolute neutrophil count (10^9/L)	4.44 (0.5-17.5)	
Absolute lymphocyte count (10^9/L)	1.81 (0.9-3.1)	
Absolute monocyte count (10^9/L)	0.51 (0.1-1.2)	
Hemoglobin level (g/L)	124 (67.7-150)	
Platelet count (10^9/L)	339.5 (207-696)	

ECOG PS: Eastern Cooperative Oncology Group performance status; g/L: gram per liter; mg/L: milligram per liter
*Missing: bone marrow involvement =3 (7%)
[a] m-IPI: adverse factors for m-IPI (stage-modified IPI) included age >60 years, elevated serum LDH, performance status (PS)≥2, Lugano stage ≥II_2, ≥1 extranodal site involvement (excluding stomach)

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Table 2. Univariate analysis (Cox regression) of main prognostic factors for overall survival and progression-free survival. For each continuous variable the hazard ratio (HR) and its confidence interval (95% CI) are given together with the *p*-value

Continuous variables (N=42)	Overall survival			Progression-free survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	2.654	0.895-7.871	0.079	0.951	0.905-1.000	0.049
Serum albumin (g/L)	0.863	0.762-0.976	0.019	0.872	0.778-0.977	0.018
Beta-2 microglobulin (mg/L)	1.324	1.052-1.666	0.017	1.262	1.025-1.554	0.028
Absolute neutrophil count (10^9/L)	1.334	1.094-1.627	0.004	1.360	1.145-1.615	<0.001
Absolute lymphocyte count (10^9/L)	0.451	0.110-1.847	0.269	0.483	0.141-1.659	0.248
Absolute monocyte count (10^9/L)	1.007	1.003-1.012	0.003	1.005	1.001-1.009	0.006
Hemoglobin level (g/L)	0.981	0.947-1.017	0.302	0.976	0.947-1.006	0.116
Platelet count (10^9/L)	1.006	1.000-1.012	0.038	1.005	1.000-1.011	0.039

Table 3. The best cut-off values determined by ROC curve analysis predicting for overall survival

Variables (N=42)	Overall survival			
	Sensitivity	Specificity	AUC	95% CI
Serum albumin ≤33.9 g/L	0.67	0.83	0.82	0.64-0.94
Beta-2 microglobulin >2.5 mg/L	0.88	0.45	0.67	0.49-0.81
Absolute neutrophil count >5.95×10^9/L	0.63	0.77	0.70	0.53-0.84
Absolute lymphocyte count ≤1.77×10^9/L	0.75	0.57	0.64	0.47-0.79
Absolute monocyte count >0.518×10^9/L	1.00	0.63	0.84	0.69-0.94
Hemoglobin level ≤105 g/L	0.50	0.88	0.63	0.46-0.78
Platelet count >335×10^9/L	1.00	0.59	0.75	0.59-0.87

Table 4. The best cut-off values determined by ROC curve analysis predicting for progression-free survival

Variables (N=42)	Progression free survival			
	Sensitivity	Specificity	AUC	95% CI
Serum albumin ≤37.8 g/L	0.86	0.69	0.81	0.63-0.93
Beta-2 microglobulin >2.5 mg/L	0.91	0.5	0.71	0.54-0.84
Absolute neutrophil count >7.0×10^9/L	0.60	0.93	0.79	0.63-0.90
Absolute lymphocyte count ≤1.77×10^9/L	0.80	0.61	0.64	0.47-0.79
Absolute monocyte count >0.518×10^9/L	0.90	0.64	0.78	0.61-0.89
Hemoglobin level ≤108 g/L	0.60	0.87	0.69	0.53-0.83
Platelet count >335×10^9/L	0.91	0.61	0.73	0.57-0.85

Prognostic significance of platelet counts

The median PC at diagnosis was 339.5×10^9/L (range, 207 – 696×10^9/L) and 11 patients had a count above the upper normal level (440×10^9/L). No association between median PC and m-IPI score risk groups was established. As a continuous variable, the PC was significantly associated with OS and PFS (**Table 2**).

The most discriminative PC cut-off value on the ROC curve was >335×10^9/L predicting for OS (**Table 3**) and PFS (**Table 4**), respectively. PC>335×10^9/L were observed in 47.6% patients and were associated with the advanced (IV) stage of the lymphoma, additional extranodal lymphoma involvement, elevated LDH and ANC levels, poor PS ≥ 2, higher m-IPI (≥2) scores and lower SA levels (p=0.006; p=0.04; p=0.048, p=0.049, p=0.01, p=0.035, and p=0.001, respectively) (**Table 6**).

After dichotomization by the most discriminative cut-off values, PC>335×10^9/L predicted for shorter OS and PFS **(Figs 2A, 2B)**. The 5-year OS was 95.5% in PC≤335×10^9/L patients compared to 65% with higher counts (p=0.013), whereas the 5-year PFS was 90.9% in patients with

Table 5. Clinical laboratory characteristics according to the absolute monocyte count (AMC) in PG-DLBCL patients

Variable	AMC>0.518×10^9/L (n=18)	AMC≤0.518×10^9/L (n=24)	*p*-value
Male gender (%)	61.1	45.8	0.37
Age >60 (%)	38.9	37.5	1.00
Advanced stage–IV (%)	33.3	25	0.73
Additional extranodal involvement (%)	33.3	25	0.73
Elevated LDH (%)	55.6	20.8	0.12
Performance status ≥2 (%)	38.9	29.2	0.53
m-IPI score ≥2 (%)	50	29.2	0.21
Median serum albumin (g/L)	38.3	39.9	0.68
Median β_2-microglobulin (mg/L)	2.8	3.2	1.00
Median absolute neutrophil count (10^9/L)	5.02	3.8	0.29
Median absolute lymphocyte count (10^9/L)	1.66	1.87	0.52
Median hemoglobin level (g/L)	121	124	0.44
Median platelet count (10^9/L)	335	324	1.00

PC≤335×10^9/L compared to 60% with higher counts (p=0.023).

Since the components of the m-IPI are important prognostic factors in DLBCL, we included components of the m-IPI in a univariate analysis with best cut-off values predicted by ROC analysis for SA, B2M, ANC, AMC, ALC, PC, Hb, and gender as dichotomized variables. As summarized in **Table 7**, only the number of extranodal sites, AMC, SA, LDH, PC, and Hb level are independently significant prognostic factors for OS, with HR of 9.69 (95% CI 1.95-48.33, p=0.006), 11.49 (95% CI 1.41-93.55, p=0.023), 0.15 (95% CI 0.03-0.84, p=0.03), 5.74 (95% CI 1.16-28.48, p=0.032), 0.11 (95% CI 0.01-0.91, p=0.041) and 0.21 (95% CI 0.05-0.86, p=0.031), respectively.

Regarding PFS, only PS, number of extranodal sites, AMC, ANC, LDH, PC, and Hb level were independently significant with HR of 3.6 (95% CI 1.01-12.82, p=0.048), 7.58 (95% CI 1.94-29.52, p=0.004), 6.93 (95% CI 1.47-32.73, p=0.014), 6.69 (95% CI 1.73-25.97, p=0.006), 4.93 (95% CI 1.27-19.13, p=0.021), 5.05 (95% CI 1.07-23.82, p=0.041) and 0.19 (95% CI 0.06-0.67, p=0.009), respectively (**Table 7**).

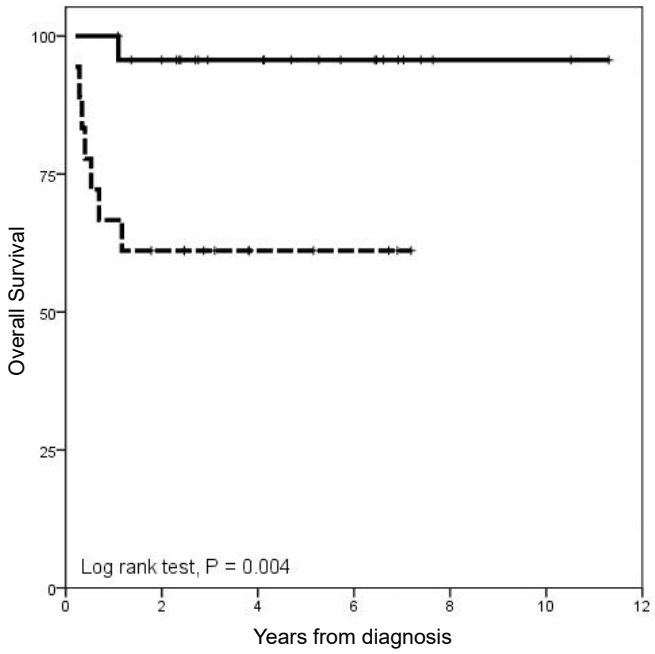
Multivariate analysis of the main prognostic variables

A backward selection, using a significance level of 0.05 for dropping variables, was employed to build a Cox proporti-

Table 6. Clinical laboratory characteristics according to the platelet count (PC) in PG-DLBCL patients

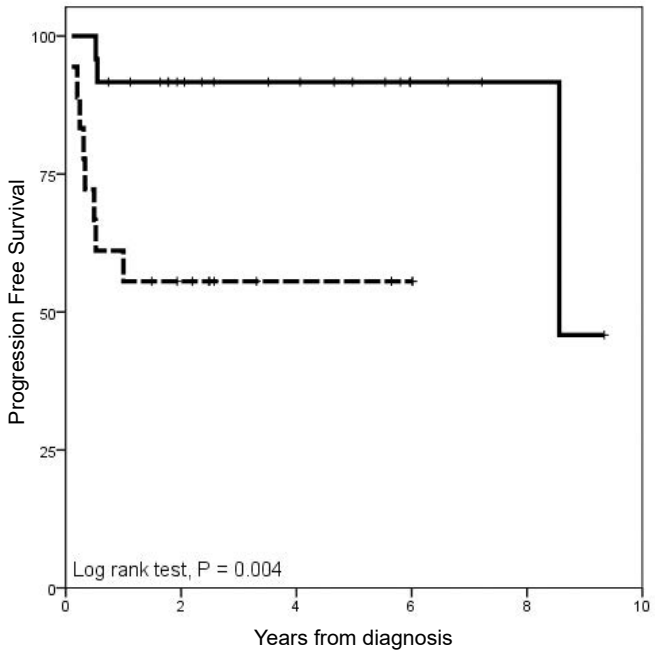
Variable	PC>335×10^9/L (n=20)	PC≤335×10^9/L (n=22)	*p*-value
Male sex (%)	45	59	0.35
Age >60 (%)	40	36.4	1.00
Advanced stage – IV (%)	50	9.1	0.006
Extranodal involvement (%)	45	13.6	0.04
Elevated lactate dehydrogenase (%)	55	20	0.048
Performance status ≥ 2 (%)	50	18.2	0.049
m-IPI score ≥2 (%)	60	18.2	0.01
Median serum albumin (g/L)	34.8	41.4	0.035
Median β_2-microglobulin (mg/L)	3.5	2.65	0.19
Median absolute neutrophil count (10^9/L)	6.91	3.46	0.001
Median absolute lymphocyte count (10^9/L)	1.77	1.81	1.00
Median absolute monocyte count (10^9/L)	0.51	0.49	1.00
Median hemoglobin level (g/L)	115.5	127.5	0.23

(A) Kaplan-Meier estimates of overall survival according to the absolute monocyte count (AMC)



Number at risk							
——— AMC≤0.518×109/L	24	20	14	9	2	2	0
– – – AMC>0.518×109/L	18	10	4	3	0	0	0

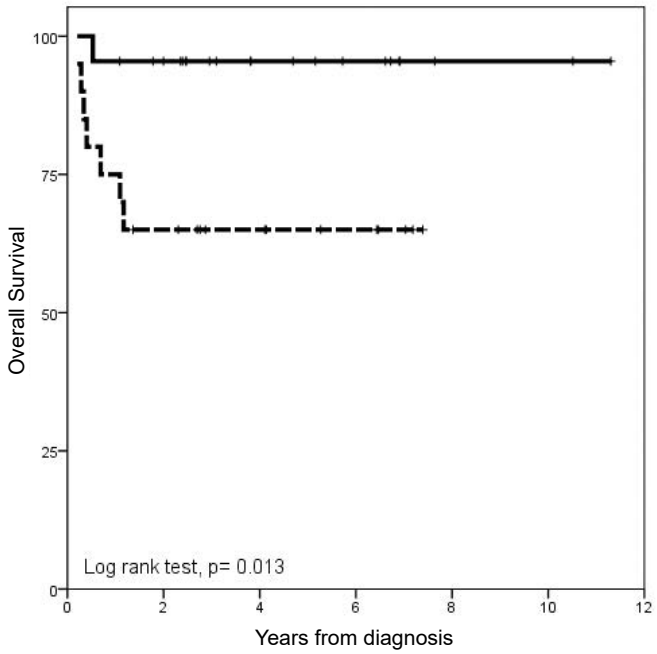
(B) Kaplan-Meier estimates of progression-free survival according to the absolute monocyte count (AMC)



Number at risk						
——— AMC≤0.518×10^9/L	24	16	12	4	2	0
– – – AMC>0.518×10^9/L	18	8	3	2	0	0

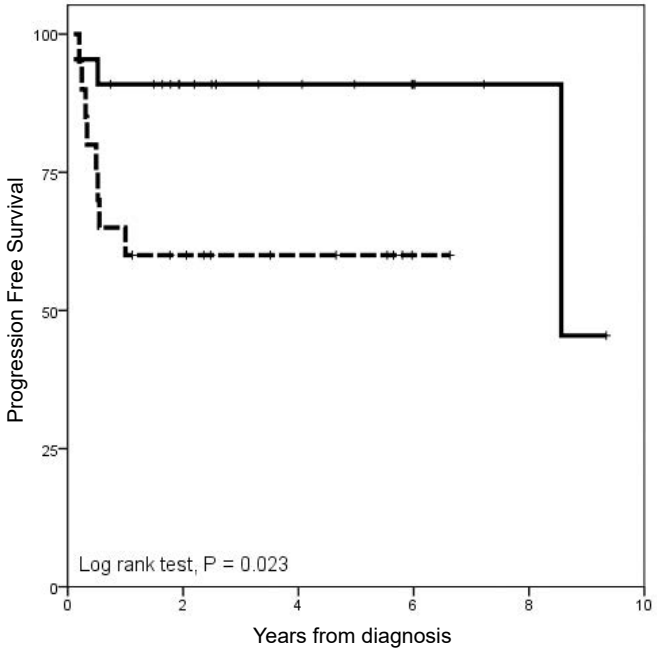
Figure 1. Outcomes of patients according to absolute monocyte count (AMC) at presentation.

(A) Kaplan-Meier estimates of overall survival according to the platelet count (PC)



Number at risk							
——— PC≤335×10^9/L	22	18	10	7	2	2	0
– – – PC>335×10^9/L	20	12	8	5	0	0	0

(B) Kaplan-Meier estimates of progression-free survival according to the platelet count (PC)



Number at risk						
——— PC≤335×10^9/L	22	14	9	5	2	0
– – – PC>335×10^9/L	20	10	6	1	0	0

Figure 2. Outcomes of the patients according to the platelet count (PC) at presentation.

onal hazards model **(Table 8)**, starting from the model with all the prognostic variables identified by univariate analysis of OS (number of extranodal sites >1, AMC >0.518×10^9/L, SA >33.9 g/L, elevated LDH, platelet count >335×10^9/L and hemoglobin level >105 g/L). The m-IPI score was not included as a specific variable because the significant factors contributing to this index were already present as individual parameters. The resulting final model comprised of AMC and PC that maintained a significant impact on OS with HR of 16.68 (95% CI 2.02–137.93, p=0.009) and 13.42 (95% CI 1.63–110.82, p=0.016), respectively. This model was also able to predict PFS **(Table 8)**.

Table 7. Univariate analysis (Cox regression) of the main prognostic factors for overall and progression-free survival

Variables	Overall survival			Progression free survival		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
≤60 years >60 years	0.22	0.03-1.77	0.15	0.16	0.02-1.25	0.08
Sex						
Male Female	2.79	0.56-13.81	0.21	2.59	0.69-9.79	0.16
ECOG PS						
<2 ≥2	4.13	0.98-17.34	0.053	3.6	1.01-12.82	0.048
Stage						
Early Advanced	4.36	0.54-35.45	0.169	1.67	0.44-6.31	0.452
Extranodal sites						
≤ 1 > 1	9.69	1.95-48.33	0.006	7.58	1.94-29.52	0.004
Absolute monocyte count						
≤ 0.518×10^9/L > 0.518×10^9/L	11.49	1.41-93.55	0.023	6.93	1.47-32.73	0.014
Absolute neutrophil count						
> 5.95×10^9/L ≤ 5.95×10^9/L	0.27	0.06-1.13	0.072	6.69	1.73-25.97	0.006
Absolute lymphocyte count						
≤ 1.77×10^9/L > 1.77×10^9/L	3.29	0.67-16.37	0.144	0.22	0.05-1.01	0.052
Serum albumin						
≤ 33.9 g/L > 33.9 g/L	0.15	0.03-0.84	0.03	0.24	0.05-1.07	0.061
β_2-microglobulin						
≤ 2.5 mg/L > 2.5 mg/L	0.19	0.02-1.55	0.12	7.08	0.89-56.03	0.064
LDH						
Normal Elevated	5.74	1.16-28.48	0.032	4.93	1.27-19.13	0.021
Platelet count						
≤ 335×10^9/L > 335×10^9/L	0.11	0.01-0.91	0.041	5.05	1.07-23.82	0.041
Hemoglobin level						
≤ 105 g/L > 105 g/L	0.21	0.05-0.86	0.031	0.192	0.06-0.67	0.009

Table 8. Multivariate analysis of the main prognostic factors: Cox regression model generated by backward selection of the significant variables identified by univariate analysis of OS and PFS (number of extranodal sites >1, absolute monocyte count >0.518×10^9/L, elevated LDH, platelet count >35×10^9/L and hemoglobin level <105 g/L). The additional prognostic factors for PFS were ECOG PS >2 and ANC >5.95×10^9/L

Variable	Overall survival		Progression free survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Absolute monocyte count > 0.518×10^9/L	16.68 (2.02–137.93)	0.009	14.15 (1.78-112.93)	0.012
Platelet count > 335×10^9/L	13.42 (1.63–110.82)	0.016	11.77 (1.47-94.13)	0.020

The AMC/PC prognostic index identifies poor-risk patients and provides additional prognostic information when superimposed on the m-IPI.

We tried to build a simple prognostic index (PI) which does not contribute to the m-IPI score. We combined the dichotomized AMC and PC to generate the AMC/PC PI and stratified patients into three risk groups: low-risk (AMC≤0.518×10^9/L and PC≤335×10^9/L), intermediate-risk (AMC≤0.518×10^9/L or PC≤335×10^9/L) and high-risk (AMC>0.518×10^9/L and PC>335×10^9/L) populations. High risk PG-DLBCL patients identified by AMC and PC had significantly higher rate of advanced (IV) stage of the lymphoma, additional extranodal lymphoma involvement, elevated LDH levels, poor PS ≥ 2, m-IPI (≥2) scores and higher ANC levels (p=0.005; p=0.004; p=0.002, p=0.02, p<0.001, and p=0.004, respectively) **(Table 9)**.

OS and PFS were analyzed using the AMC/PC PI and the m-IPI. The median OS was not reached for the low and intermediate-risk groups identified by AMC/PC PI with an estimated 5-year OS of 100% and 90.9%, respectively. Similarly, using the m-IPI, the estimated 5-year OS among low-, low/intermediate- and high/intermediate-risk patients was 93.3%, 100%, and 66.7%, respectively. In contrast, the median OS was only 0.4 years (95% CI 0.15-0.89 years), with an estimated 5-year OS of 25% among high-risk patients identified using the AMC/PC PI **(Fig. 3a)**, compared to 1.09 years (95% CI 0.27–1.92 years) median OS and 38.1% 5-year OS in the high-risk group defined by the m-IPI **(Fig. 3b)**.

The estimated 5-year PFS among low- and intermediate-risk patients stratified by the AMC/PC PI was 100% and 81.8%, respectively **(Fig. 3c)**, which was comparable to the m-IPI approach, defining a 5-year PFS among low-, low/intermediate- and high/intermediate-risk patients of 86.7%, 100% and 55.6%, respectively **(Fig. 3d)**.

The AMC/PC PI identified a group of poor-risk patients with a median PFS of 0.33 years (95% CI 0.08–0.59 years) and an estimated 5-year PFS of 25%. Similarly, the median PFS was 0.5 years (95% CI 0.41–0.69 years) and the estimated 5-year PFS was 42.9% among high-risk patients identified using the m-IPI. Clearly, the AMC/PC PI was able to risk-stratify patients in a manner comparable to the m-IPI.

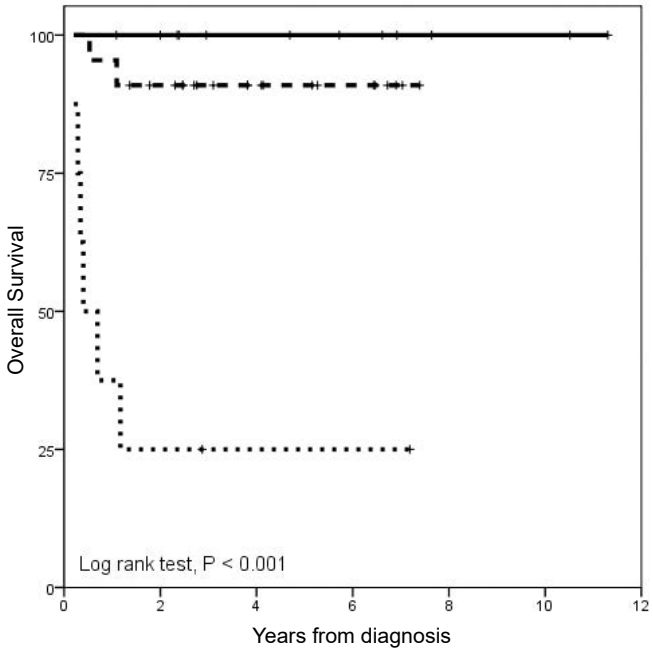
Furthermore, the AMC/PC PI retained statistical significance at multivariate analysis on OS and PFS after controlling for the m-IPI **(Table 10)**.

Therefore, we sought to determine whether it may provide additional prognostic information when combined with the m-IPI. To test this possibility, low-, intermediate-, and high-risk patients were segregated by the m-IPI. Due to the lack of death events, no statistics could be calculated in the low-risk group.

Table 9. Relationships between clinical laboratory characteristics and the three groups of PG-DLBCL patients

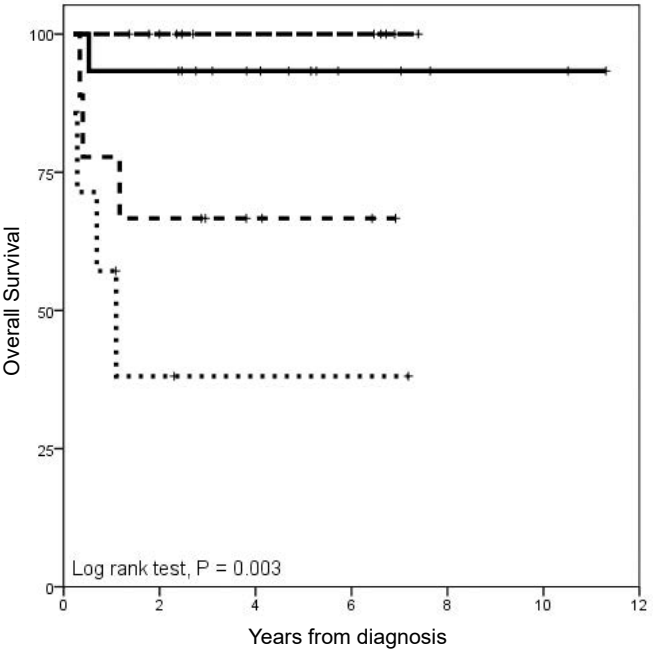
Variable	Low risk (n=11)	Intermediate risk (n=23)	High risk (n=8)	*p*-value
Male sex (%)	63.6	43.5	62.5	0.61
Age >60 (%)	36.4	39.1	37.5	0.99
Advanced stage – IV (%)	18.2	17.4	75	0.005
Extranodal involvement (%)	27.3	13.0	75	0.004
Elevated LDH (%)	9.1	34.8	87.5	0.002
Performance status ≥ 2 (%)	27.3	21.7	75	0.02
m-IPI score ≥2 (%)	27.3	21.7	100	<0.001
Median serum albumin (g/L)	41.75	37.9	33.9	0.11
Median β_2-microglobulin (mg/L)	2.9	2.8	3.25	0.24
Median absolute neutrophil count (10^9/L)	3.36	4.61	7.23	0.004
Median absolute lymphocyte count (10^9/L)	1.81	1.88	1.65	0.72
Median hemoglobin level (g/L)	127.5	123.5	114.5	0.33

3a



Number at risk							
—— low	12	10	7	5	2	2	0
– – – intermediate	22	18	10	6	0	0	0
····· high	8	2	1	1	0	0	0

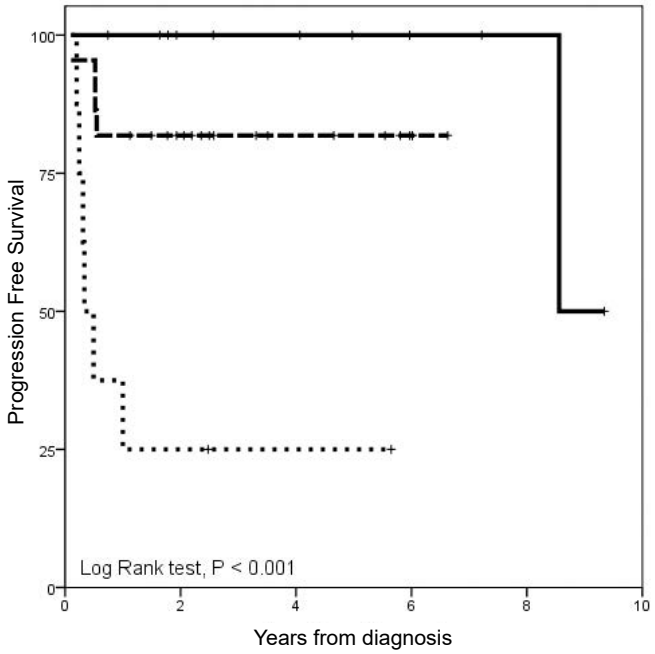
3b



Number at risk							
—— low	15	14	9	4	2	2	0
– – – low-intermediate	11	8	5	5	0	0	0
- - - - - high-intermediate	9	6	3	2	0	0	0
····· high	7	2	1	1	0	0	0

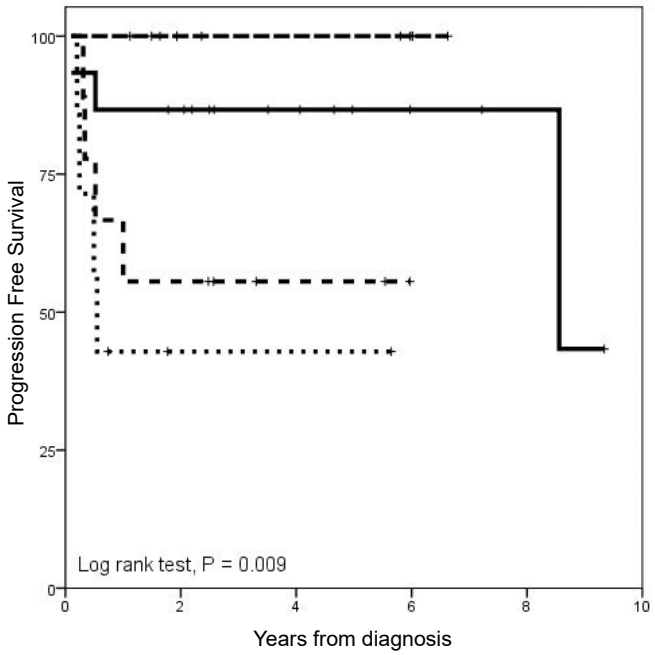
Figure 3. Kaplan-Meier estimates of overall (**a, b**) and progression-free (**c, d**) survival for the entire patients' cohort stratified by the AMC/PC prognostic index (**a, c**) and by the modified International Prognostic Index (**b, d**) are shown.

3c



Number at risk						
—— low	12	8	7	3	2	0
– – – intermediate	22	14	7	3	0	0
····· high	8	2	1	0	0	0

3d



Number at risk						
—— low	15	12	7	3	2	0
– – – low-intermediate	11	6	5	3	0	0
----- high-intermediate	9	5	2	0	0	0
····· high	7	1	1	0	0	0

Figure 3. Kaplan-Meier estimates of overall (**a, b**) and progression-free (**c, d**) survival for the entire patients' cohort stratified by the AMC/PC prognostic index (**a, c**) and by the modified International Prognostic Index (**b, d**) are shown.

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The intermediate-risk (high-intermediate and low-intermediate were combined) patients (n=20) identified by the m-IPI were subsequently risk stratified using the AMC/PC prognostic index **(Fig. 4)**.

In this group, the 5-year OS was 100% among low- and intermediate-risk patients identified by the AMC/PLC PI **(Fig. 4)**. In contrast, 20% of patients identified by the m-IPI as 'intermediate-risk', upon further risk stratification by the AMC/PC PI, had dismal outcomes, with a median OS of only 4.8 months (95% CI 0–34 months) and 2-year OS of 25% (p<0.001). The 5-year PFS was 100% and 90% among low- and intermediate-risk patients by the AMC/PLC PI **(Fig. 5)**. However, 25% patients upon further risk stratification by the AMC/PC PI, had poor outcomes, with a median PFS of 3.9 months (95% CI 0–29 months) and 2-year PFS of 25% (p=0.003).

Due to the low number of patients, no prognostic significance could be established for AMC/PC PI in high-risk m-IPI group.

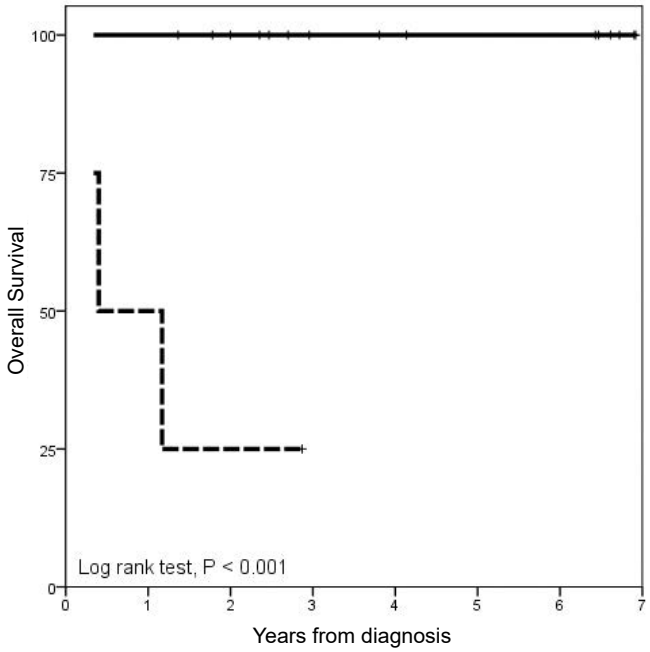
DISCUSSION

The results of the present study indicated that the PC and AMC at diagnosis may be used as biomarkers for predicting survival in PG-DLBCL patients treated with R-CHOP. The elevated PC and AMC correlated with a worse prognosis in the PG-DLBCL and identified high-risk patients. To the best of our knowledge, no other studies assessing the prognostic impact of PC and AMC in PG-DLBCL patients treated with R-CHOP have been published to date.

The gold standard for risk stratification and prognosis in patients with PG-DLBCL continues to be m-IPI. However, other prognostic markers have been investigated to

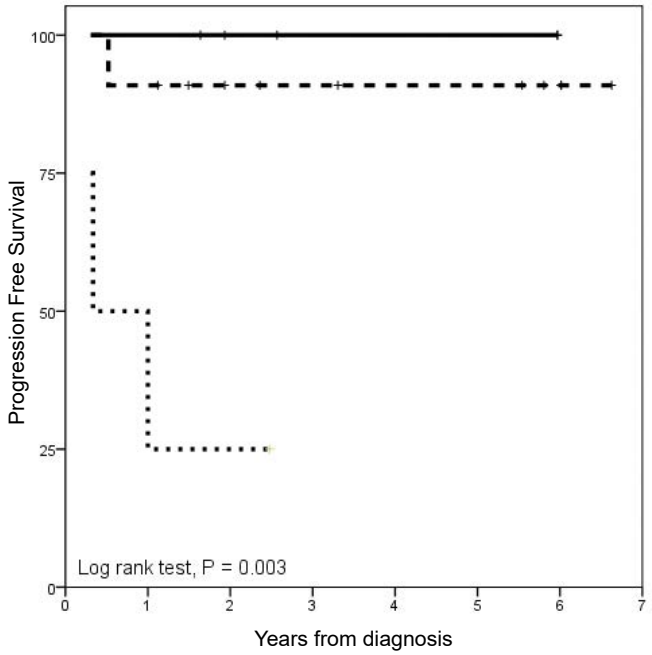
Table 10. Cox regression models estimating the effect of the AMC/PC prognostic index on overall and progression-free survival after controlling for the m-IPI

Variable	Overall survival		Progression free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
AMC/PC prognostic index	10.12 (1.48-69.37)	0.018	6.88 (1.54-30.75)	0.012
m-IPI	1.29 (0.54-3.09)	0.555	1.11 (0.58-2.15)	0.750



Number at risk								
low and int.	16	16	13	9	8	7	7	0
high	4	2	1	0	0	0	0	0

Figure 4. Patients identified by the m-IPI as low-intermediate/high-intermediate risk were further stratified into low- and intermediate- (solid line) or high-risk (dashed line) groups by the AMC/PC prognostic index (Kaplan-Meier estimates of overall survival are shown).



Number at risk								
—— low	5	5	3	2	2	2	2	0
– – – inter	11	10	7	6	5	5	3	0
····· high	4	2	1	0	0	0	0	0

Figure 5. Patients identified by the m-IPI as low-intermediate/high-intermediate-risk were further stratified into low (solid line), intermediate (dashed line) or high-risk (dotted line) groups by the AMC/PC prognostic index (Kaplan-Meier estimates of progression-free survival are shown).

improve prediction of survival in patients with PG-DLBCL. Many of the researchers have focused on immunohistochemistry correlates (germinal center type versus activated B-cell type), molecular and gene expression profiling tests that are cumbersome, difficult to interpret and are cost prohibitive.[11,26] In contrast, the measurement of AMC and PC is a simple test that could be easily employed in regular clinical practice.

In the present study, the elevated PC was significantly associated with advanced tumor clinical stage (stage IV), additional extranodal lymphoma involvement, lower SA levels, higher ANC and unfavourable m-IPI score. An elevated PC represented an independent and powerful predictor of poor outcome. The prognostic value of PC was retained at multivariate analysis after controlling for the main other adverse prognostic indicators. Our results are in line with data provided by previously reported studies that confirm the adverse prognostic impact of elevated PC in cancer patients.[27-30, 51-55] However, according to other DLBCL studies, thrombocytopenia rather than thrombocytosis is a poor prognostic factor.[20] This could be explained by the different patients' populations and different rates of bone marrow infiltration.

The prognostic impact of PC might be associated with a more aggressive biology related to earlier hematogenous dissemination in cases with elevated counts. Platelets activated by tumor cells play major roles in aiding and abetting tumor progression. First, platelets can help tumor cells survive immune surveillance in the blood circulation. Activated platelets may act as protective "cloaks" for circulating tumor cells, shielding them from immune destruction by natural killer cells.[31,32] This process is mediated by platelet-derived growth factor and transforming growth factor β.[33,34] Hematogenous dissemination of tumor cells can also be facilitated by "platelet mimicry," in which tumor cells acquire a phenotype that closely resembles that of platelets'. In addition, platelets and vascular endothelium may facilitate tumor cell extravasation and seeding through adhesion molecules P- and L-selectins, a hypothesis supported by the observation that tumor metastases are reduced in mice lacking them.[35,36]

In the present study, the elevated AMC represented an independent, powerful predictor of unfavourable outcome that is highly consistent with previously published studies in solid tumors and lymphomas.[10,37-41,51-55] The exact pathophysiology for the association between high monocyte counts and poor prognosis is not well understood. However, being an important player in immunity, monocytes might play a role in the chronic inflammation which has already been associated with the induction of stomach can-

cer and the link with cancer progression has been known for over a century.[42,43] Besides, chronic inflammation is associated with suppression of anti-tumor immune responses and a tumor microenvironment that favours tumor progression. So firstly, AMC may relate to the insidious progression of cancer disease involving activation of innate immune system through mobilization of monocytes to tissue macrophages that develops an inflammatory state associated with increased risk of cancer and mortality.[44,45] Monocytes play a key role in innate immunity, constitute nearly 5% of the circulating white blood cell pool, and exhibit a short half-life in the circulation of a few hours.[46] Secondly, the monocytes, known as the key component of inflammation system, might directly stimulate cancer cell growth by producing various proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor. Tumor-associated macrophages (TAMs) appear to play a crucial role in the tumor microenvironment and can educate and control invading leukocytes to promote angiogenesis, viability, motility, and invasion.[44,45]

From a practical point of view, the proposed AMC/PC PI derived from a CBC at diagnosis is widely available and may be easily incorporated into clinical practice. Furthermore, the AMC/PC PI provided prognostic information independently of that included in the m-IPI and was able to provide additional prognostic information when used in conjunction with the m-IPI. This was particularly true for low-intermediate- and high-intermediate-risk patients who collectively accounted for approximately 50% of the patients in our series. When patients identified as intermediate risk by the m-IPI were further risk stratified by the AMC/PC prognostic index, 20% of these patients were identified as high risk.

In addition, our findings might raise certain issues of reassessment of therapeutic approaches in particular patient categories. With drug development, treatment for PG-DLBCL has shifted from surgery to gastric preservation methods, including immunochemotherapy in order to aid organ conservation. The addition of rituximab to CHOP regimen has improved the therapeutic outcomes, and the superiority of RCHOP has been confirmed by several clinical studies.[47-49] However, R-CHOP proved to be of limited value in high risk patients stratified by the AMC/PC prognostic index. The evidence linking both platelets and myeloid-lineage cells with hematogeneous dissemination, and in this study with poor PFS and OS, raises the possibility that strategies which reverse elevated PC or deplete tumorigenic myeloid-lineage cells may represent novel therapeutic approaches in DLBCL. Despite this, to date no specific platelet function targeted therapy has been included in standard cancer treatment. Therapeutic strategies targeting myeloid-lineage cells, including myeloid-derived suppressor cells, are currently being investigated in solid tumors and may warrant further investigation in NHL.[50]

CONCLUSIONS

In the present study, we found that pretreatment routine hematological parameters including PC and AMC correlated with prognosis in PG-DLBCL patients treated with R-CHOP. Although this study has certain limitations since it was a retrospective analysis and a single-center study, the AMC/PC PI demonstrates that variables related to the host immune response and the tumor microenvironment are worth consideration when generating prognostic indices in NHL, as these variables may provide additional prognostic information independently from conventional patient- and tumor-specific factors. The low cost, easy accessibility and reproducibility of CBC are other features promoting its use in clinical practice. To confirm these findings, larger, prospective, randomized studies are required in future.

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Абсолютное количество моноцитов и тромбоцитов может предоставить дополнительную прогностическую информацию у пациентов с первичной диффузной крупноклеточной В-клеточной лимфомой желудка, получавших лечение ритуксимабом и CHOP

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Резюме

Введение: Первичная диффузная крупноклеточная В-клеточная лимфома желудка (PG-DLBCL) является наиболее распространённым гистологическим подтипом первичной лимфомы желудка. Стандартным лечением пациентов с PG-DLBCL является комбинация иммунохимиотерапии на основе ритуксимаба (R-CHOP). Недавно было показано, что различные факторы, связанные с хозяином, имеют важное прогностическое значение при неходжкинской лимфоме. Однако данные об их прогностическом влиянии на PG-DLBCL ограничены.

Цель: Оценить прогностическое влияние панели простых, рентабельных лабораторных переменных, которые легко применить в повседневной лабораторной среде для пациентов с PG-DLBCL, прошедших лечение R-CHOP, с целью выявления тех, кто попадает в категории повышенного риска.

Материалы и методы: Мы ретроспективно оценили возможный прогностический эффект различных лабораторных маркеров у пациентов с PG-DLBCL, прошедших лечение R-CHOP в период с 2004 по 2014 год и находившихся под наблюдением в том же заведении.

Результаты: Примерная 5-летняя общая выживаемость (ОВ) и выживаемость без прогрессирования (ВБП) всей группы составила 80.9% и 78% соответственно. Абсолютное количество моноцитов и тромбоцитов в одновариантном анализе предсказывало ВБП и ОВ при анализе как непрерывных и дихотомических переменных. В многофакторном анализе, проведенном с факторами, включенными в международный прогностический индекс с измененной стадией (stage-modified International Prognostic Index(m-IPI), абсолютное количество моноцитов и тромбоцитов оставалось независимыми предикторами ВБП и ОВ. Ввиду данного обстоятельства, абсолютные показатели количества моноцитов и тромбоцитов были объединены для создания прогностического индекса, который идентифицирует пациентов с особенно плохой общей выживаемостью.

Заключение: Этот прогностический индекс не зависел от m-IPI и мог предоставить дополнительную прогностическую информацию для лучшей стратификации этих пациентов.

Ключевые слова

клетки, гематологические злокачественные новообразования, иммунотерапия, прогноз