

Novel prognostic scoring system for diffuse large B-cell lymphoma

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Abstract. The objective of the present study was to evaluate the prognostic values of platelet count (PLT) and platelet to lymphocyte ratio (PLR) in diffuse large B-cell lymphoma (DLBCL), creating a novel prognostic scoring system. A total of 309 patients with newly diagnosed DLBCL were retrospectively analyzed. Receiver operating characteristic analysis was used to determine the optimal threshold values for PLT and PLR, which were $250 \times 10^9/l$ and 170, respectively. The patients with $PLT \geq 250 \times 10^9/l$ and $PLR \geq 170$ experienced significantly decreased overall survival (OS) ($P < 0.001$) and progression-free survival (PFS) times ($P = 0.003$, $P < 0.001$) In multivariate analysis, PLR was a significant prognostic factor for OS ($P < 0.001$) and PFS ($P = 0.003$) time, whereas PLT was not a risk factor for PFS or OS time. According to the results of Cox regression analysis, a novel prognostic scoring system was created that combined PLR and β_2 -microglobulin level with International Prognostic Index value or age-adjusted International Prognostic Index value and the patients were divided into three groups: i) Low-risk patients with a $PLR < 170$, International Prognostic Index (IPI) < 2 scores or age-adjusted International Prognostic Index (aaIPI) = 0 and normal β_2m ; ii) high-risk patients with a $PLR \geq 170$, IPI ≥ 4

or aaIPI = 3 and high level of β_2m ; and iii) intermediate-risk patients. The novel score predicted 5-year OS rates of 86.4, 54.1 and 21.1% in the low-, intermediate- and high-risk groups, respectively ($P < 0.001$). This novel prognostic scoring system may aid the evaluation of patient prognosis and guide treatment.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common histological form of non-Hodgkin's lymphoma (NHL), accounting for 30-40% of all adult NHLs (1,2). A diagnosis is made according to the morphology and immunophenotype of B cells (3). First-line management of DLBCL is a combination of chemotherapy drugs, rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) (4). The International Prognostic Index (IPI) (5) and age-adjusted International Prognostic Index (aaIPI) (6) serve important functions in daily practice to determine the treatment strategies and prognosis of individual cases. Neither the IPI nor the aaIPI identifies a risk group with $< 50\%$ chance of survival (6). Thus, novel prognostic models are highly sought after. Inflammatory cells and cytokines located in tumors are more likely to contribute to cancer growth, spread, progression and immunosuppression than they are to mount an effective host antitumor activity (7-10). The inflammatory response can be represented by the level of serum neutrophils, lymphocytes, platelets, C-reactive protein and albumin (7) Previously, several combinations of these factors, including the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) have been reported to be useful prognostic factors in various malignant tumors (8,11-14). However, to date, no reports have investigated whether platelet count (PLT) and PLR are prognostic factors for DLBCL. The objective of this study was to investigate the prognostic ability of PLT and PLR in patients with DLBCL, and to obtain a novel prognostic scoring system for these metrics in order to predict the prognosis of the patients.

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Abbreviations: DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; aaIPI, age-adjusted International Prognostic Index; ALC, absolute lymphocyte count; PLT, platelet count; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; LDH, lactate dehydrogenase; β_2m , β_2 -microglobulin; OS, overall survival; PFS, progression-free survival

Key words: diffuse large B-cell lymphoma, platelet, platelet-lymphocyte ratio, β_2 -microglobulin, prognostic

Patients and methods

Patients and clinicopathological variables. The clinical characteristics of 309 patients (including 186 males and 123 females) diagnosed with DLBCL between March 2009 and

February 2015 at Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) were retrospectively analyzed. All patients who were treated with R-CHOP-21 [rituximab (375 mg/m²) on day 1; cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²) and vincristine (1.4 mg/m²; maximal dose, 2 mg) on day 2; and prednisone (100 mg/day) on days 2 to 6] were diagnosed with DLBCL via pathological analysis. The dose and number of chemotherapy cycles were decided by physicians. The mean age of all patients was 58 years (range, 16-90 years). The median follow-up for the study was 47 months (range, 1-89 months). All patients included in the study were diagnosed with untreated DLBCL. Patients who had a previous history of malignancy, immunosuppression or previous treatment were excluded from the study. The available clinical parameters included age, gender, germinal center B-cell-like or non-germinal center B-cell-like disease, systemic B symptoms, Ann Arbor stage (15), IPI or aaIPI, hemoglobin (HGB), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute neutrophil count (NEUT), PLT, serum albumin, serum lactate dehydrogenase level (LDH: Normal range 114-285 U/l), β_2 -microglobulin (β_2m : Normal range 0.97-2.64 mg/l). The cell of origin was analyzed by immunohistochemistry. ALC, AMC, NEUT and PLT were obtained from pre-treatment CBC counts. According to IPI or aaIPI value, the patients were divided into four groups: i) Low-risk patients with IPI <2 scores or aaIPI=0; ii) low-intermediate risk patients with IPI=2 or aaIPI=1; iii) intermediate-high risk patients with IPI=3 or aaIPI=2; iv) high risk patients with IPI=4,5 or aaIPI=3. This study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital and was conducted in accordance with the Declaration of Helsinki.

Time from diagnosis of DLBCL to mortality from any cause was designated OS time. The time from diagnosis to lymphoma relapse, progression or mortality due to any cause was designated PFS time. The aim of the present study was to assess the effect of PLT, NLR, LMR and PLR on OS and PFS.

Statistical analysis. Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA). Receiver operating characteristic (ROC) curves was used to determine the optimal threshold values of ALC, PLT, NLR, LMR and PLR. Patient characteristics were compared between PLR <170 vs. PLR \geq 170 using the Pearson χ^2 test. The survival curves were determined using the Kaplan-Meier method and the log-rank test. Multivariate analysis, which used Cox's proportional hazards model, was performed for the variables identified as statistically significant in univariate analysis to exclude confounding factors. A novel prognostic scoring system was then created to combine these factors, which were identified as statistically significant. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics of the patients with DLBCL. This study included 309 patients with newly diagnosed DLBCL. The mean age was 58 years (range, 16-90 years). A total of 186 patients were male, and 181/309 (58.6%) patients remained

alive at the time of writing. Among the 128 mortalities, 123 individuals succumbed to disease recurrence, 4 individuals succumbed to infectious shock and 1 individual succumbed to respiratory failure. Baseline clinical and laboratory parameters are presented in Table I.

Selection of the best threshold values of ALC, PLT and PLR for DCBCL patients. ROC curve analyses determined the optimal threshold values for ALC, PLT and PLR. The optimal ALC threshold value was $1.45 \times 10^9/l$, with an area under the curve (AUC) value of 0.640 [95% confidence interval (CI), 0.578-0.703; $P < 0.001$; Fig. 1A]. ROC curve analysis identified $250 \times 10^9/l$ as the threshold value of PLT for predicting survival with an AUC of 0.622 (95% CI, 0.559-0.685; $P < 0.001$; Fig. 1B). The threshold value of PLR was 170, with an AUC of 0.640 (95% CI, 0.577-0.703; $P < 0.001$; Fig. 1C).

Association of PLR with the clinical characteristics in patients with DLBCL. ROC curve analyses determined that the sum of the specificity and the sensitivity was the largest when PLR was 170, with an AUC of 0.640 (95% CI, 0.577-0.703; $P < 0.001$). Therefore, a PLR of 170 was chosen as the threshold for division into two groups. Patients were divided into two groups: PLR <170 group or PLR \geq 170 group. A total of 144 patients (46.6%) had a PLR <170 and 165 patients (53.4%) had a PLR \geq 170. Compared with the patients with a PLR <170, the patients with PLR \geq 170 were significantly associated with the presence of B syndromes, increased Ann-Arbor stages (15), high-intermediate risk or high risk (IPI \geq 3, aaIPI \geq 2), decreased albumin levels, decreased HGB levels and increased LDH. However, there was no significant association between PLR and age, gender, subtype or β_2m (Table II).

Prognostic significance of PLT and PLR. Univariate analysis revealed that an age \geq 60 years ($P < 0.001$), the presence of B symptoms ($P = 0.001$), stage III-IV disease ($P < 0.001$), high-intermediate risk or high risk ($P < 0.001$), decreased albumin levels ($P < 0.001$), decreased HGB levels ($P < 0.001$), ALC ($P < 0.001$), NLR ($P = 0.019$), LMR ($P < 0.001$), increased LDH levels ($P < 0.001$) and β_2m ($P < 0.001$) were poor prognostic factors (Table III). Patients with a PLT $\geq 250 \times 10^9/l$ experienced a significantly decreased OS rate (5-year OS rate, 50.0 vs. 70.7%; $P < 0.001$ Fig. 2A) and PFS (5-year PFS rate, 45.7 vs. 61.5%; $P = 0.003$ Fig. 2B) than those with PLT <250 $\times 10^9/l$. The OS and PFS rate in patients with a PLR \geq 170 were significantly decreased compared with those with a PLR <170 at diagnosis (5-year OS rate, 41.8 vs. 77.1%, $P < 0.001$ Fig. 2C; 5-year PFS rate, 35.8 vs. 70.6%, $P < 0.001$, Fig. 2D). Furthermore, via multivariate analysis, age, IPI or aaIPI risk groups, β_2m and PLR were identified to be independent prognostic factors for OS, whereas age, Ann-Arbor stage and PLR may independently predict poor PFS (Table IV).

Prognostic significance of the PLR and β_2m combined with IPI or aaIPI. As the diagnosis and treatment of DLBCL has improved, the ability of IPI or aaIPI to differentiate between risk groups, particularly high-risk groups, has declined (Fig. 3A-D). Thus, according to the results of the Cox regression analysis, a novel score was created combining the PLR and β_2m with IPI

Table I. Patient characteristics.

Baseline characteristics	Patients, n (%)
Age	
<60	178 (57.6)
≥60	131 (42.4)
Sex	
Male	186 (60.2)
Female	123 (39.8)
B symptoms	
Absent	209 (67.6)
Present	100 (32.4)
Ann Arbor stage	
I-II	177 (57.3)
III-IV	132 (42.7)
IPI or aaIPI risk group	
Low-risk	112 (36.2)
Low-intermediate risk	95 (30.8)
High-intermediate risk	56 (18.1)
High risk	46 (14.9)
Subtype	
GCB	125 (40.5)
n-GCB	184 (59.5)
Albumin, g/l	
≥35	259 (83.8)
<35	50 (16.2)
HGB, g/l	
≥110	232 (75.1)
<110	77 (24.9)
ALC, x10 ⁹ /l	
≥1.45	172 (55.7)
<1.45	137 (44.3)
PLT, x10 ⁹ /l	
≥250	186 (60.2)
<250	123 (39.8)
NLR	
≥2.9	125 (40.5)
<2.9	184 (59.5)
LMR	
≥2.65	193 (62.5)
<2.65	116 (37.5)
PLR	
≥170	165 (53.4)
<170	144 (46.6)
LDH (114-285 U/l)	
>Normal	128 (41.4)
≤Normal	181 (58.6)
β2m (0.97-2.64 mg/l)	
>Normal	131 (42.4)
<Normal	178 (57.6)

IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; GCB, germinal center B-cell like; nGCB, non-germinal center B-cell like; HGB, hemoglobin; ALC, the absolute lymphocyte count; PLT, platelet count; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; LDH, lactate dehydrogenase; β2m, β2-microglobulin.

Table II. Clinical comparison between patients with PLR<170 and PLR≥170.

Baseline characteristics	PLR<170 ^a , n	PLR≥170 ^b , n	P-value
Age, years			>0.999
<60	83	95	
≥60	61	70	
Sex			0.728
Male	85	101	
Female	59	64	
B symptoms			<0.001
Absent	115	94	
Present	29	71	
Ann Arbor stage			<0.001
I-II	101	76	
III-IV	43	89	
IPI or aaIPI risk group			<0.001
Low-risk	75	37	
Low-intermediate risk	43	52	
High-intermediate risk	14	43	
High-risk	12	33	
Subtype			>0.999
GCB	59	67	
n-GCB	85	98	
Albumin, g/l			<0.001
≥35	137	122	
<35	7	43	
HGB, g/l			<0.001
≥110	132	100	
<110	12	65	
LDH (114-285 U/l)			<0.001
>Normal	39	89	
≤Normal	105	76	
β2m (0.97-2.64 mg/l)			0.728
>Normal	42	89	
<Normal	102	76	

^an=144; ^bn=165. IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; GCB, germinal center B-cell like; n-GCB, non-germinal center B-cell like; HGB, hemoglobin; LDH, lactate dehydrogenase; β2m, β2-microglobulin.

or aaIPI, 309 patients were split into three groups: i) Low-risk patients with a PLR <170, IPI <2 scores or aaIPI=0 and normal β2m; ii) high-risk patients with a PLR ≥170, IPI ≥4 or aaIPI=3 and high level of β2m; and iii) intermediate-risk patients. This novel score predicted a 5-year OS rate of 86.4, 54.1 and 21.1% in the low-, intermediate- and high-risk groups, respectively (P<0.001; Fig. 3E). The estimated 5-year PFS rate with this stratification was: 81.4% for the low-risk group, 47.0% for the intermediate-risk group and 21.1% for the high-risk group (P<0.001; Fig. 3F).

Discussion

DLBCL is a highly aggressive NHL with varied clinical manifestations and variable patient prognosis. IPI is the widely

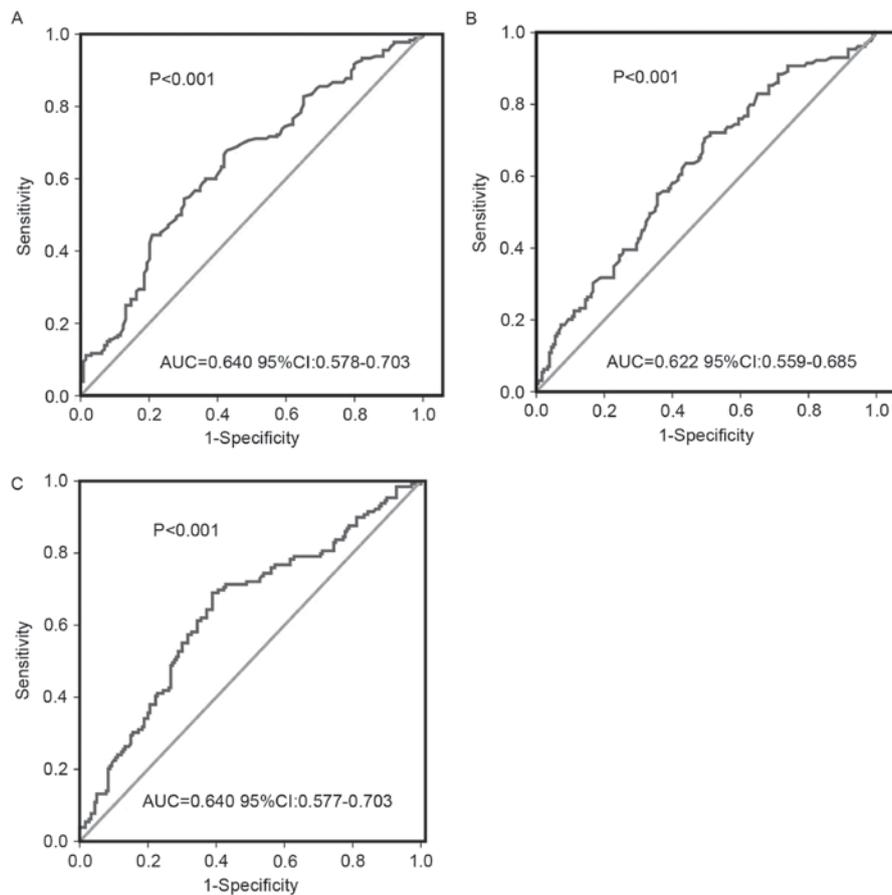


Figure 1. Receiver operating characteristic curve, AUC and 95% CI for the (A) absolute lymphocyte count, (B) platelet count and (C) platelet-lymphocyte ratio at diagnosis. AUC, area under curve; CI, confidence interval.

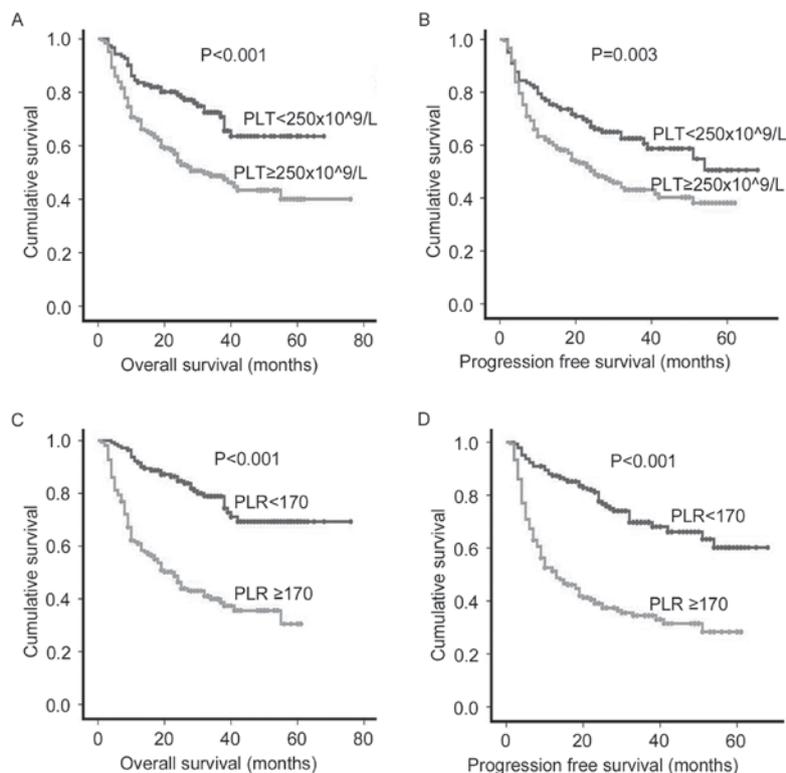


Figure 2. Kaplan-Meier curve of (A) overall survival according to the PLT ($P < 0.001$) and (B) progression free survival according to the PLT ($P = 0.003$). Kaplan-Meier curve of (C) overall survival according to the PLR ($P < 0.001$) and (D) progression-free survival according to the PLR ($P < 0.001$). PLT, platelet count; PLR, platelet-lymphocyte ratio.

Table III. Analysis of prognostic factors for OS and PFS (univariate analysis) in 309 patients with DLBCL.

Baseline characteristics	OS	P-value	PFS	P-value
Age, years		<0.001		<0.001
<60	68.5		61.8	
≥60	44.3		38.5	
Sex		0.836		0.715
Male	58.6		51.6	
Female	57.7		52.5	
B symptoms		0.002		0.001
Absent	63.2		57.2	
Present	48.4		41.0	
Ann Arbor stage		<0.001		<0.001
I-II	72.3		65.5	
III-IV	39.4		33.6	
IPI or aaIPI risk groups		<0.001		<0.001
Low-risk	77.7		72.3	
Low-intermediate risk	62.1		51.6	
High-intermediate risk	36.8		29.8	
High risk	28.9		29.5	
Subtype		0.552		0.155
GCB	62.1		58.9	
n-GCB	55.5		47.0	
Albumin, g/l		<0.001		<0.001
≥35	62.9		57.0	
<35	34.0		26.1	
HGB, g/l		<0.001		<0.001
≥110	63.8		57.6	
<110	41.6		35.1	
ALC (x10 ⁹ /l)		<0.001		<0.001
≥1.45	69.8		64.3	
<1.45	43.8		36.5	
PLT (x10 ⁹ /l)		<0.001		0.003
≥250	50.0		45.7	
<250	70.7		61.5	
NLR		0.019		0.003
≥2.9	51.2		43.2	
<2.9	63.0		57.9	
LMR		<0.001		<0.001
≥2.65	66.3		60.4	
<2.65	44.8		37.9	
PLR		<0.001		<0.001
≥170	41.8		35.8	
<170	77.1		70.6	
LDH (114-285 U/l)		<0.001		<0.001
>Normal	43.2		63.5	
≤Normal	69.1		35.4	
β2m (0.97-2.64 mg/l)		<0.001		<0.001
>Normal	39.7		33.6	
≤Normal	71.9		65.5	

IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; GCB, germinal center B-cell like; n-GCB, non-germinal center B-cell like; HGB, hemoglobin; ALC, the absolute lymphocyte count; PLT, platelet count; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; LDH, lactate dehydrogenase; β2m, β2-microglobulin.

accepted prognostic factor index for patients with DLBCL (5). The addition of rituximab to conventional chemotherapy has led to a marked improvement in patient survival rates (4). As a result, the ability of IPI or aaIPI to differentiate between risk groups, particularly high-risk groups, has declined (5). The revised International Prognostic Index is unable to identify a risk group with a <50% chance of survival (6). This means that more sensitive prognostic factors are required. Inflammation is recognized as a major hallmark of cancer. As early as 1863, Rudolf Virchow, who suggested that lymphoreticular infiltration reflected the origin of cancer at sites of chronic inflammation, identified a connection between inflammation and cancer (16). Subsequently, numerous studies have provided evidence that the host inflammatory responses serve a critical function in various aspects of cancer, including cancer initiation, promotion, progression and metastasis (7,17-19). Previously, a number of inflammatory markers have been proposed to have potential for use as predictors of OS and PFS for solid tumors (8,12,20-23). The present study identified that NLR, LMR and PLR may be able to predict the prognosis of patients with DLBCL.

Monocytes and neutrophils, which are important components in the active defense system, are potent regulators of macrophages, mast cells and epithelial cells, and serve an important function in inflammatory events (16). These cell types are able to differentiate into tumor-associated macrophages in tumor tissue, which undergo tumor-promotion and M2-like macrophage polarization and secrete angiogenic factors, including interleukin-8, vascular endothelial growth factor (VEGF) and fibroblast growth factor, then induce further tumor angiogenesis and progression (24,25). Furthermore, monocyte-derived cells may provide nutritional factors that directly promote the growth and survival of malignant tumors (17-19).

Lymphocytes are the basic components of the immune system; they can induce cytotoxic cell death and produce cytokines in cancer cells (26,27). Lymphocytopenia impairs the antitumor immune response of the host, which in turn promotes tumor expansion and leads to a poor patient prognosis.

Tumors require the formation of new blood vessels to provide nutrients and oxygen for continued lesion growth. Platelets release VEGF upon their activation, thus promoting angiogenesis (28). Platelet activation also protects tumor cells from natural killer cells, and platelets support spontaneous metastasis (22-23). Platelet-derived lysophosphatidic acid enhances bone metastatic growth and progression, and platelet-released factors may serve a function in tumor progression (29). Therefore, these results provide evidence that platelet counts may serve as inflammatory biomarkers and could aid the prediction of the prognosis of patients.

β2m is a human leukocyte antigen-class I molecule that is expressed on the membrane of almost all nucleated cells. Studies have reported that β2m, which regulates p21-activated kinases, VEGF and fatty acid synthase-mediated growth and survival signaling pathways, is a growth factor and signaling molecule in cancer cells (30,31); it serves a critical function in the proliferation, apoptosis and metastasis of cancer cells (30,32). Furthermore, β2m is a useful prognostic factor in multiple types of cancer, including breast (33), gallbladder (34), prostate

Table IV. Multivariate analysis of prognostic factors for survival in testing set.

Characteristics	Overall survival		Progression-free survival	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age	<0.001	2.410 (1.678-3.460)	<0.001	2.022 (1.488-2.823)
B symptoms	0.348	1.209 (0.814-1.797)	0.185	1.277 (0.889-1.834)
Ann Arbor stage	0.123	1.441(0.906-2.294)	0.038	1.575 (1.026-2.418)
IPI or aaIPI risk groups	0.009	1.402 (1.088-1.806)	0.161	1.183 (0.935-1.495)
Albumin	0.413	1.231 (0.748-2.026)	0.478	1.183 (0.743-1.885)
HGB	0.354	0.807 (0.513-1.269)	0.627	0.900 (0.589-1.375)
PLT	0.221	1.321 (0.846-2.064)	0.852	0.961 (0.636-1.454)
ALC	0.080	1.472 (0.955-2.270)	0.067	1.456 (0.937-2.178)
NLR	0.314	0.815 (0.548-1.213)	0.764	0.945 (0.652-1.369)
LMR	0.139	0.758 (0.525-1.095)	0.083	0.738 (0.523-1.040)
PLR	<0.001	0.327 (0.205-0.521)	<0.001	0.418 (0.274-0.640)
LDH	0.240	1.294 (0.842-1.989)	0.036	1.536 (1.028-2.295)
β 2m	0.043	1.499 (1.012-2.219)	0.133	1.327 (0.917-1.920)

OS, overall survival; PFS, progression-free survival; IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; GCB, germinal center B-cell like; n-GCB, non-germinal center B-cell like; HGB, hemoglobin; ALC, the absolute lymphocyte count; PLT, platelet count; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; LDH, lactate dehydrogenase; β 2m, β 2-microglobulin; CI, confidence interval.

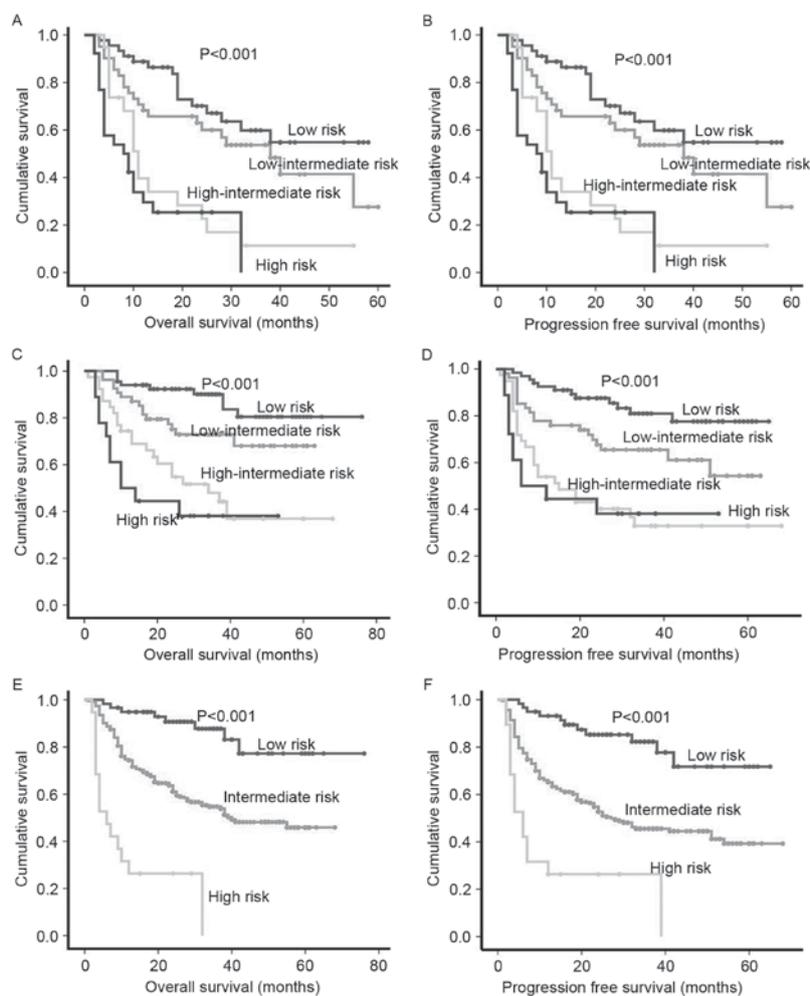


Figure 3. Kaplan-Meier curve of (A) OS times according to IPI risk group ($P < 0.001$) and (B) PFS times according to IPI risk group ($P < 0.001$). Kaplan-Meier curve of (C) OS times according to aaIPI risk group ($P < 0.001$) and (D) PFS times according to aaIPI risk group ($P < 0.001$). Kaplan-Meier curve of (E) OS times according to risk group combined with PLR and β 2M ($P < 0.001$) and (F) PFS times according to risk group combined with PLR and β 2M ($P < 0.001$). OS, overall survival; PFS, progression free survival; IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; PLR, platelet-lymphocyte ratio; β 2M, β 2-microglobulin.

and lung cancer (31), chronic lymphocytic leukemia (35) and follicular lymphoma (36). In the present study, an increased level of $\beta 2m$ was associated with poor patient prognosis in DLBCL.

In summary, PLT and PLR were associated with poor prognosis in patients with DLBCL. The NLR and LMR at diagnosis, as biomarkers combining an estimate of host immune and tumor microenvironment, were previously hypothesized to be powerful prognostic factors in patients with newly diagnosed DLBCL (37); the results of the present study confirmed this. Furthermore, it was identified that PLR was an independent predictor of survival in patients who were newly diagnosed with DLBCL. Additionally, it was identified that the patients who have a poor prognosis may be divided through a novel prognostic scoring system (PLR and $\beta 2m$ combined with IPI or aaIPI), which is of great significance for the evaluation of prognosis and guiding treatment.

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