ORIGINAL RESEARCH

The Value of Prognostic Nutritional Index (PNI) on Newly Diagnosed Diffuse Large B-Cell Lymphoma Patients: A Multicenter Retrospective Study of HHLWG Based on Propensity Score Matched Analysis

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Introduction: Immunonutritional status is associated with the survival of DLBCL. This multicenter retrospective study aimed to explore the prognostic value of Prognostic Nutrition Index (PNI) in DLBCL patients by using propensity score matched analysis (PSM).

Methods: A total of 990 DLBCL cases were recruited from 5 centers of Huaihai Lymphoma Working Group (HHLWG). A 1:1 PSM analysis was performed using the nearest-neighbor method, with a caliper size of 0.02. Cox regression analysis was used to examine factors associated with survival.

Results: The median age at diagnosis was 62 years and 52.5% were males, with the 3-y overall survival of 65.1%. According to the MaxStat analysis, 44 was the optimal cut-off point of PNI. After PSM analysis, a total of 282 patients in PNI < 44 group could be propensity matched to PNI ≥ 44 patients, creating a group of 564 patients. Multivariable analysis revealed that PNI, age, central nervous system involvement and International Prognostic Index (IPI) were independent prognostic factors for DLBCL. Kaplan–Meier analysis indicated that patients with low PNI in Ann Arbor Stage (III/VI), ECOG (<2), IPI (LR+LIR), GCB, and BCL-2 negative groups had a poor prognosis.

Discussion: PNI could accurately stratify the prognosis of DLBCL after PSM analysis.

Keywords: diffuse large B-cell lymphoma, prognostic nutrition index, propensity score matched, prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma with high heterogeneity and aggressiveness. Although 60–70% patients can be cured by the current standard of care in the frontline setting, the majority of the remaining patients will experience refractory and relapse. Clinical variables based prognostic systems, such as International Prognostic Index (IPI)[1] and NCCN-IPI,[2] can achieve prognostic stratification of DLBCL patients. However, these indices do not take the nutritional status of patients into account.

Malnutrition is a common problem in cancer patients, occurring in up to 80% of patients with advanced stage.[3] It will affect the response to treatment and lead to poor quality of life in cancer patients.[4] Assessment of systemic nutritional status was

refined by the introduction of the prognostic nutrition index (PNI), a continuous variable based on serum albumin concentration and total lymphocyte count in peripheral blood.[5] PNI was originally designed to assess perioperative immunonutritional status and surgical risk in patients undergoing gastrointestinal surgery.[6,7] Several studies have confirmed that PNI has prognostic value in a variety of malignant tumors.[6,8,9] Yao et al suggested that PNI was a significant indicator of extranodal natural killer/T cell lymphoma.[10] Besides, there were a few reports exploring the prognostic role of PNI in DLBCL with limitations of small sample size and single-center data.[11–13]

Confounding factors always weaken the accuracy and objectivity of retrospective studies. Propensity score analysis (PSM) is commonly used to overcome selection bias, adjust the confounding factors, improve the comparability between groups by increasing the evidence level in retrospective studies, and mimic randomization on observed covariates.[14–18]

In this retrospective study, based on multicenter data of DLBCL from Huaihai Lymphoma Working Group (HHLWG) in China, we firstly carried out this PSM analysis to evaluate the prognostic value of PNI in DLBCL patients.

Materials and Methods
Patients
A total of 990 newly diagnosed DLBCL patients from 2008 to 2021 were recruited, and all pathological biopsies were double blinded and reviewed by at least two pathologists. Exclusion criteria: 1) patients with other malignant tumors; 2) patients with special types of lymphoma (primary central nervous system lymphoma, primary mediastinal DLBCL, transformed DLBCL); 3) patients with other immune diseases; 4) diseases that affect the lymphocyte level and albumin level of patients (such as hepatitis, cirrhosis, chronic kidney disease). During admission, the following variables were considered: age, gender, lactate dehydrogenase (LDH), hemoglobin (HB), platelet (PLT), albumin (Alb), lymphocyte count (LYC), red blood cell count (RBC), Ki-67, presence of bulky disease, B symptoms, β_2-microglobulin (β_2-MG), ECOG PS and Ann Arbor stage.

Follow-Up and Endpoints
Follow-up was conducted by consulting inpatient medical records and making phone calls. We followed up all the patients until July 28, 2021 or the death of patients. Overall survival (OS) was calculated as the interval between the time of diagnosis and death from any cause or the last follow-up. The survival status of all patients was confirmed with death records or a telephone call to next of kin (if patient died during the follow-up) or to the patients themselves. Study approval was obtained from the independent Ethics Committees of each participating center in HHLWG and met with the Helsinki Declaration.

Assessment of PNI
PNI, based on serum albumin and lymphocytes, is a scoring system that reflects the nutritional status and immune status of patients. It is calculated using the formula:[7]

$$PNI = 10 \times albumin(g/dL) + 0.005 \times lymphocyte\,count(/mm^3)$$

Statistical Analysis
Data were presented as numbers (percentages) for categorical variables and median (interquartile range, IQR) for all continuous variables. Differences in clinical factors were analyzed by using χ^2 test. PNI was transformed into a categorical variable by MaxStat analysis (titled as Maximally Selected Rank Statistics). The Cox proportional hazard model was used to analyze the univariate association between prognostic factors and OS. All variables with $P < 0.05$ in univariable analysis were kept in the multivariate analysis by using backward selection for the best predictor set, and Akaike Information Criteria (AIC) was used to evaluate the model. All the statistical tests were two-sided, and the statistical significance was set at $P < 0.05$.

A 1:1 propensity score-matched (PSM) analysis was performed using the nearest-neighbor method, with a caliper size of 0.02 to identify the impact of PNI on DLBCL. To reduce selection bias and confounding factors, the propensity score was calculated using logistic regression analysis. The standardized mean difference (SMD) was measured to determine the balance between the two groups before and after PSM. The SMD cut-off value was <0.1, which was regarded as indicating a sufficient balance between the two groups. After 1:1 propensity score matching, continuous variables were compared using Mann–Whitney U-test, and categorical variables were compared using χ^2 test. All statistical analyses were performed by SPSS statistics for Windows, Version 22.0 (Armonk, NY: IBM corp.), R software (version 4.0.3; http://www.Rproject.org) and Stata version 15.0.

Results

Characteristics of DLBCL Patients

The characteristics of 990 DLBCL patients were detailed in Table 1. The median follow-up time was 46.133 (95% CI: 43.759–48.508) months and the median OS was 140.033 (95% CI: 70.614–209.453) months. At the end of follow-up, a total of 358 (36.1%) deaths occurred. The median age at diagnosis was 62 years (range: 10–91), with 520 (52.5%) males and 431 (43.5%) patients were younger than 60 years. A total of 261 (26.3%) patients with

Table I Associations Between PNI and Clinicopathological Factors Before and After PSM

Variables	Before Propensity Matching		P	After Propensity Matching		P
	PNI < 44	PNI ≥ 44		PNI < 44	PNI ≥ 44	
	(n = 318)	(n = 672)		(n = 282)	(n = 282)	
Age (y)	64 (56,72)	61 (51,68)	<0.001	63 (54,71)	66 (57,71)	0.093
Gender			0.221			0.174
Male	176 (55.3)	344 (51.2)		152 (53.9)	168 (59.6)	
Female	142 (44.7)	328 (48.8)		130 (46.1)	114 (40.4)	
PLT	198 (139,281)	223 (183,271)	<0.001	203 (140,282)	220 (165,261)	0.477
β2-MG	2.71 (2.63,5.11)	2.71 (2.05,4.48)	0.001	2.7 (2.5,4.5)	2.7 (2.2,1710)	0.433
NE	4.13 (2.78,6.16)	3.99 (3.04,4.98)	0.315	4.1 (2.8,6.1)	3.9 (3.1–5.0)	0.814
LDH			<0.001			0.107
Normal	121 (38.1)	454 (67.6)		113 (40.1)	158 (56.0)	
Elevated	197 (61.9)	218 (32.4)		169 (59.9)	124 (44.0)	
CNS involvement			0.083			0.259
Absence	249 (78.3)	557 (82.9)		227 (80.5)	216 (76.6)	
Presence	69 (21.7)	115 (17.1)		55 (19.5)	66 (23.4)	
BM involvement			0.001			0.835
Absence	246 (77.4)	589 (87.6)		225 (79.8)	223 (79.1)	
Presence	72 (22.6)	83 (12.4)		57 (20.2)	59 (20.9)	
Bulky			<0.001			0.148
Absence	181 (56.9)	548 (81.5)		167 (59.3)	209 (74.1)	
Presence	137 (43.1)	124 (18.5)		115 (40.7)	73 (25.9)	
ECOG			<0.001			0.431
<2	192 (60.4)	532 (79.2)		184 (65.2)	175 (62.1)	
2–4	126 (39.6)	140 (20.8)		98 (34.8)	107 (37.9)	
IPI			<0.001			0.800
LR/+LIR	130 (40.9)	495 (73.7)		130 (46.1)	127 (45.0)	
HIR/HR	188 (59.1)	177 (26.3)		152 (53.9)	155 (55.0)	
Ann Arbor stage			<0.001			0.413
I/II	94 (29.6)	378 (56.3)		92 (32.6)	83 (29.4)	
III/IV	224 (70.4)	294 (43.8)		190 (67.4)	199 (70.6)	
Cell of origin			0.154			0.554
GCB	175 (55.0)	402 (59.8)		156 (55.3)	149 (52.8)	
Non-GCB	143 (45.0)	270 (40.2)		126 (44.7)	133 (47.2)	

Abbreviations: PLT, platelet; NE, neutrophil count; LDH, lactate dehydrogenase (normal<240 U/L); CNS involvement, central nervous system involvement; BM involvement, bone marrow involvement.

B symptoms and 117 (11.8%) patients were with bulky disease. The 5-y of patients were 65.1% (Figure 1). In this study, patients received regimens of CHOP-like (n = 261), R-CHOP/R-CHOP-like (n = 601) and R-based intensive regimens (n = 128). Twenty-five patients received BTK inhibitor (BTKi), forty-four patients received methotrexate (MTX), and thirty-five patients received autologous hematopoietic stem cell transplantation (Auto-HSCT). Kaplan–Meier analysis indicated that there was no significant difference in therapeutic regimens in global comparison ($P > 0.05$). Further subgroup analysis of R-based intensive regimens also showed no difference.

The Optimal Cut-off Point for PNI Based on MaxStat

According to the maximal chi-square method, 44 was the optimal cut-off point that distinguished between two prognostic groups most effectively ($P < 0.05$, $\chi^2 = 7.28$, Figure 2).

Applying this result, the new definition of PNI < 44 was poor nutritional status group, and PNI ≥ 44 was normal nutritional status group.

Characteristics of DLBCL Patients After PSM

In this study, the Pseudo R^2 before matching was about 0.09, which decreased to less than 0.01 after matching, indicating that the overall equilibrium test could pass. After PSM, a total of 282 patients in PNI < 44 group could be propensity matched to PNI ≥ 44 patients, creating a group of 564 patients. The two groups were remarkably balanced after matching based on 8 confounding factors, as each confounding factor was no longer be significantly different ($P > 0.05$, Table 1). The absolute standard deviation of the two matched groups were <10% for all the covariates (Figure 3).

After PSM, the median OS of DLBCL patients was 34 months (95% CI: 15.042–52.824) in low PNI group and 61 months (95% CI: 31.795–90.205) in high PNI group. Ages
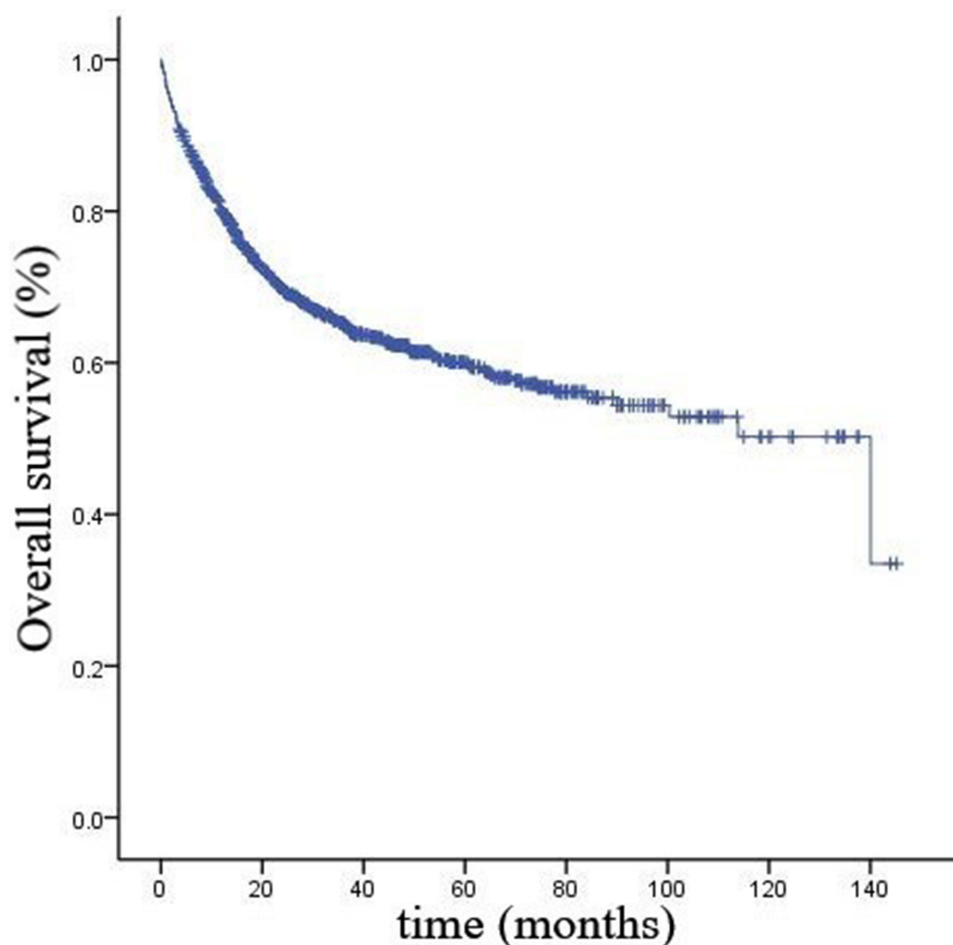
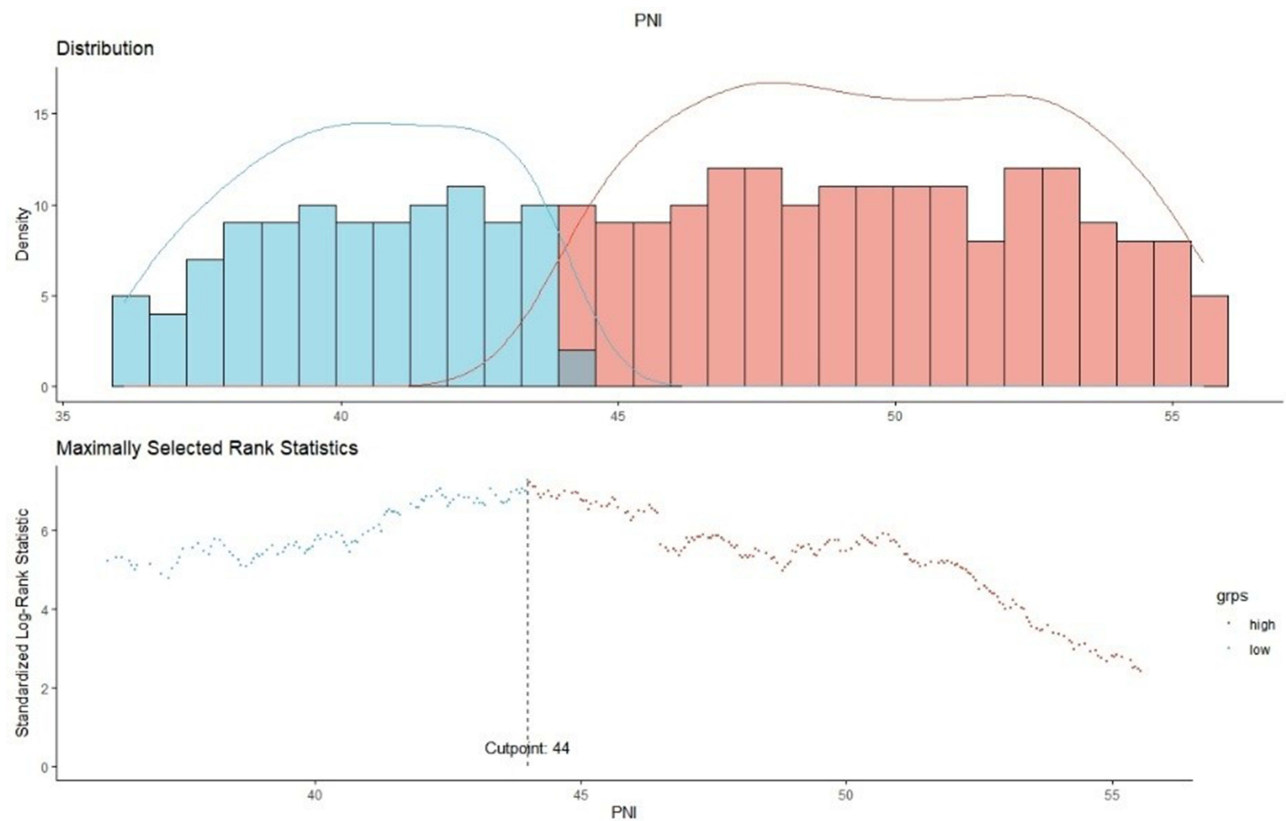**Figure 1** Overall survival of 990 DLBCL patients.

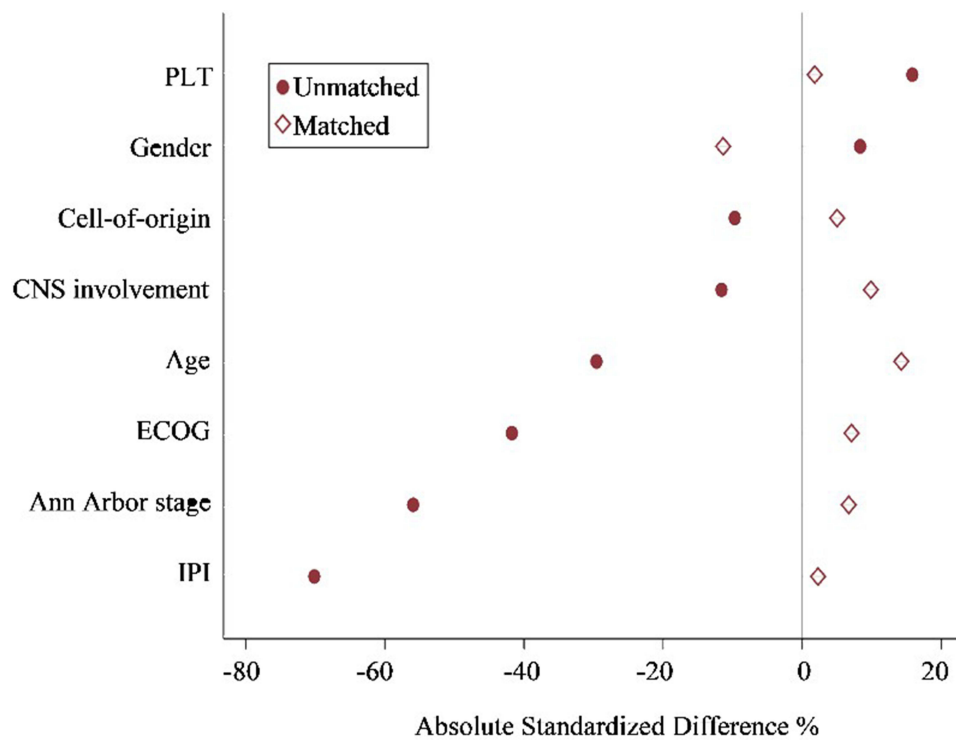**Figure 2** The optimal cut-off point for PNI by using MaxStat.

Figure 3 Impact of PNI on DLBCL after PSM.

Hazard ratio (95% confidence interval)
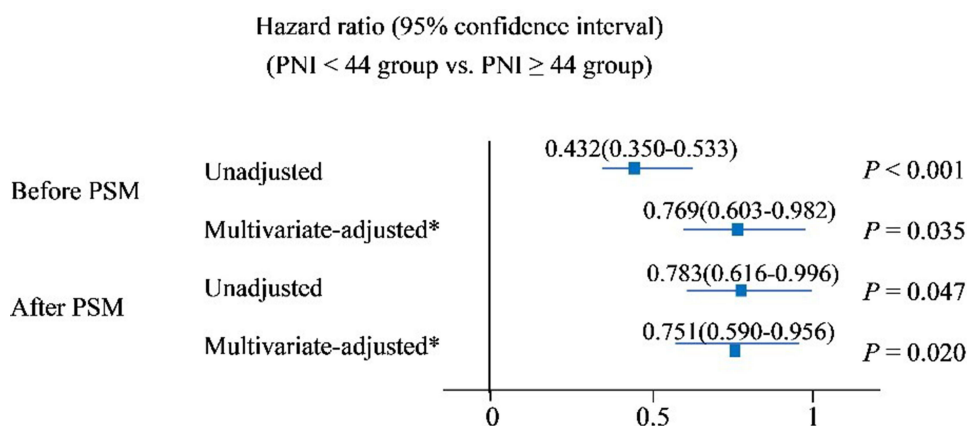(PNI < 44 group vs. PNI ≥ 44 group)

Figure 4 Predictive value of the PNI for the prognosis of DLBCL (*P < 0.05).

of patients ranged from 14 to 91 years with a median age of 65 years, of whom 244 (43.2%) patients were female. A total of 121 (27.1%) patients (21.4%) patients were with CNS involvement and 87 (15.4%) patients were with bulky disease. The characteristics of patients after PSM were detailed in Table 1.

The predictive value of the PNI < 44 group for the prognosis of DLBCL was shown in Figure 4. Compared with PNI ≥ 44, PNI < 44 was associated with poorer survival of DLBCL in unadjusted (HR = 0.432, 95% CI: 0.350–0.533; $P < 0.001$), multivariate-adjusted (HR = 0.769, 95% CI: 0.603–0.982; $P = 0.035$), and propensity score matched analyses (HR = 0.751, 95% CI: 0.590–0.956; $P = 0.020$, Figure 4).

Univariable and Multivariable Analysis of DLBCL Patients

After PSM, a univariable analysis revealed that low PNI was an adverse factor for the survival of patients (HR = 0.783, $P = 0.047$, Table 2). In addition, age, CNS involvement and IPI

appeared to be stronger predictors ($P < 0.001$). However, BCL-2, BCL-6, and cell of origin were not independent prognostic factors of DLBCL ($P > 0.05$). Multivariable analysis revealed that PNI remained an independent prognostic factor for DLBCL (HR = 0.751, $P = 0.020$). Compared to patients with low PNI (PNI < 44), patients with PNI ≥ 44 had a high 5-y OS (51.1% vs 44.8%).

Prognostic Values of PNI with Clinicopathologic Factors in DLBCL

Of 564 patients after PSM, 303 cases were positive for BCL-2, and 257 cases were positive for BCL-6. Sixty-four (11.3%) patients were with high Ki-67 score (≥0.9) and 259 (45.9%) were non-GCB. PNI in Ann Arbor Stage (III/VI), ECOG (<2), IPI (LR+LIR), GCB, and BCL-2 negative groups could re-stratify the survival of patients (Figure 5). While PNI in Ann Arbor Stage (I/II), ECOG (≥2), IPI (HLR+HR), non-GCB, BCL-2 positive group, BCL-6, Ki-67, and MYC groups could not predict the survival of patients.

Table 2 Univariable and Multivariable Analysis After 1:1 Ratio PSM

Variables	Univariable Analysis			Variables	Multivariable Analysis		
	HR	**95% CI**	**P**		**HR**	**95% CI**	**P**
PNI	0.783	0.616–0.996	0.047	PNI	0.751	0.590–0.956	0.02
Age (y)	1.025	1.015–1.036	<0.001	Age (y)	1.019	1.008–1.030	0.001
Gender	0.797	0.623–1.020	0.071	CNS involvement			
CNS involvement	2.917	2.265–3.757	<0.001	Absence			
ECOG	1.486	1.166–1.894	0.001	Presence	2.583	2.001–3.334	<0.001
IPI	2.305	1.780–2.984	<0.001	IPI			
Ann Arbor stage	1.200	0.921–1.562	0.177	LR+LIR			
PLT	1.000	0.999–1.001	0.777	HIR+HR	1.967	1.512–2.560	<0.001

Abbreviations: PLT, platelet; CNS involvement, central nervous system involvement.
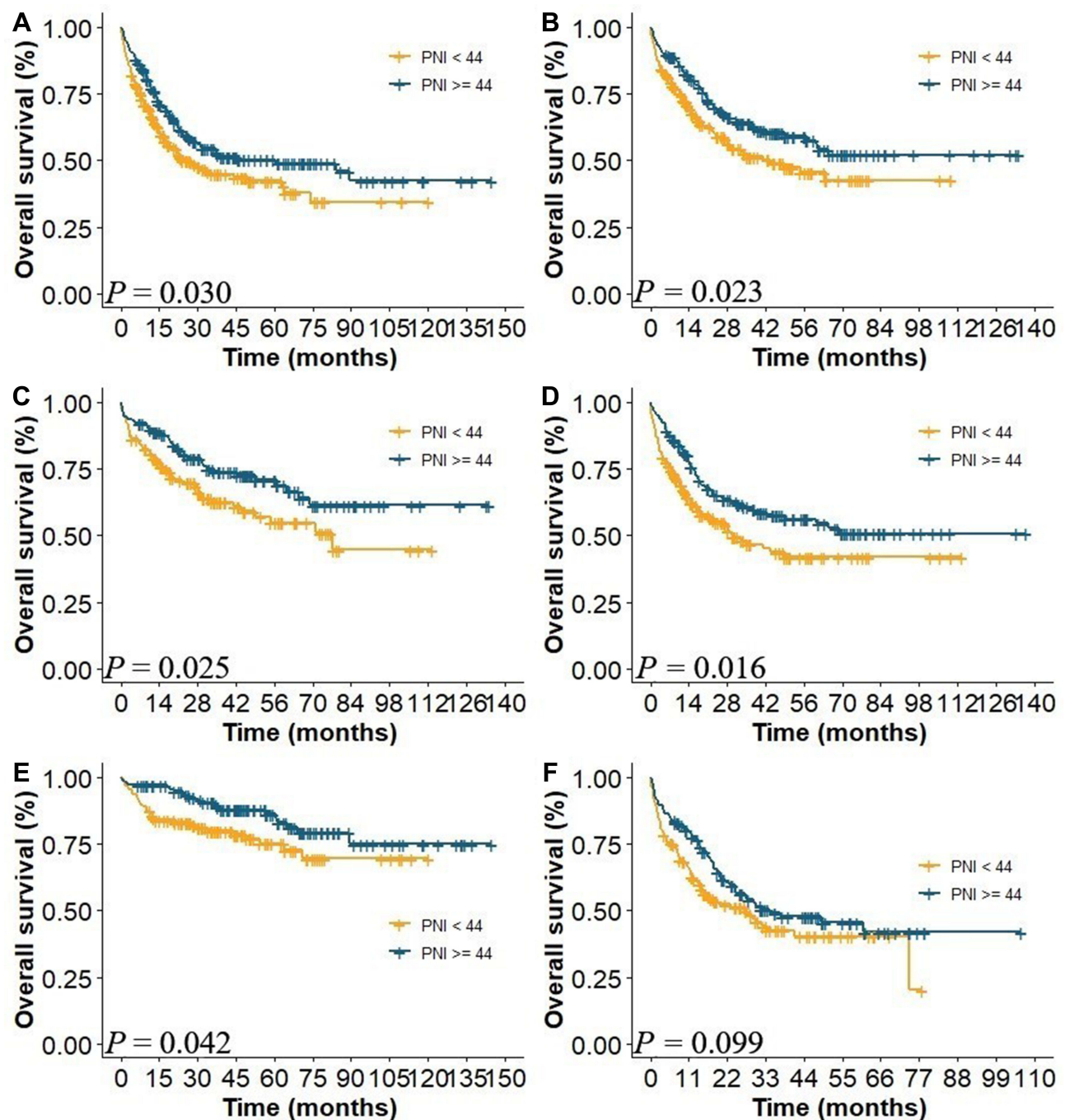
Figure 5 Kaplan-Meier survival curves of DLBCL patients. (**A**) prognosis of different PNI levels in Ann Arbor stage (III/VI) group; (**B**) prognosis of different PNI levels in ECOG (<2) group; (**C**) prognosis of different PNI levels in IPI (LR/LIR) group; (**D**) prognosis of different PNI levels in GCB group; (**E**) prognosis of different PNI levels in negative BCL-2 group; (**F**) prognosis of different PNI levels in positive BCL-6 group.

Discussion

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma with highly heterogeneous. In this retrospective multicenter study, we analyzed the value of PNI on DLBCL. To our knowledge, this is the first study evaluating the prognostic effect of PNI on DLBCL with propensity score matching analysis, and we

proved that PNI was an independent factor for patients with DLBCL.

Nutritional status is closely related to the prognosis of lymphoma patients.[19–21] Nutritional insufficiency may influence poor survival outcomes of DLBCL patients.[22] Kanemasa et al confirmed that geriatric nutritional risk index could identify a population of poor-risk DLBCL

patients by NCCN-IPI.[23] The controlling nutritional status was identified as an independent prognostic factor for OS of DLBCL patients.[24,25] PNI, a feasible tool for assessing the relationship between immunonutritional status and prognosis of patients has been widely used in acute heart failure, esophageal cancers and lymphoma.[10,26–28] In this study, we confirmed that PNI was an independent factor for predicting the survival of DLBCL, and we calculated the optimal cut-off point of PNI. According to the maximal chi-square method, 44 was the optimal cut-off point that distinguished between two prognostic groups most effectively, which was close to the results of previous studies.[11,12,29,30] However, these studies did not take confounding factors into consideration, which might misevaluate the prognostic value on DLBCL. In our study, using propensity score matched analysis, other clinical characteristics of patients were well adjusted, and no differences were confirmed between low PNI and high PNI groups. This reduces the interference of confounders on survival outcome to some extent. Multivariate analysis showed that PNI, age, CNS involvement and IPI were independent prognostic factors for OS. Patients in HIR/HR groups of IPI had poor survival, which was consistent with one of our previous studies.[31]

DLBCL is highly heterogeneous in pathological features and elements of heterogeneity are associated with the prognosis of patients. Therefore, we evaluated the values of PNI on different groups of cell-of-origin, Ann Arbor Stage, ECOG, IPI and other pathological factors. The results confirmed that PNI could not re-stratify BCL-2 positive and non-GCB groups, while PNI could re-stratify BCL-2 negative, Ann Arbor Stage (III/VI) and IPI (LR+LIR) groups. The 5-y OS for malnourished patients was 56.3% in GCB group and 55.9% in ECOG (<2) group.

In conclusion, by using propensity score matched analysis, we confirmed that adjusted PNI was an effective prognostic factor for DLBCL patients. However, due to the inherent flaw of the retrospective design, more prospective studies need to be conducted to confirm this result in the future.

Ethics Approval and Informed Consent

Study approval was obtained from the independent Ethics Committees of each center in HHLWG and met with the Helsinki Declaration. Ethics committees approved the patients or next of kin being contacted by telephone. Written, informed consent was waived, since this study used retrospective data obtained only from hospital medical records.

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Disclosure

The authors declare no conflicts of interest.

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