



Clinical impact of prognostic nutritional index in diffuse large B cell lymphoma

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Abstract

We evaluated the association between the prognostic nutritional index (PNI) and the clinical features of diffuse large B cell lymphoma (DLBCL) and developed a novel prognostic model using a nomogram including the PNI and other biomarkers for cancer cachexia. A total of 228 DLBCL patients treated with first-line R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) were retrospectively reviewed. PNI was calculated as $10 \times$ serum levels of albumin (g/dL) + $0.005 \times$ absolute lymphocyte count (/mm³). Patients were categorized into low- and high-PNI groups based on a cut-off value of 40. The nomogram for predicting overall survival (OS) was constructed using a Cox regression model. PNI was positively correlated with skeletal muscle index, body mass index, and serum levels of albumin. The low-PNI group had a lower complete response rate (60.3% vs. 87.6%), increased treatment-related toxicity, and more frequent treatment discontinuation (43.5% vs. 8.8%) than the high-PNI group. The median OS was shorter in the low-PNI group than the high-PNI group (15.6 months vs. not reached; $p < 0.001$). Multivariate Cox regression analyses showed that PNI, sarcopenia, and the international prognostic index (IPI) were independent prognostic factors for OS. The nomogram developed using this regression model showed excellent discriminatory ability for predicting OS (c-index, 0.80) compared to the IPI alone (c-index, 0.75). Low PNI was associated with adverse clinical features of DLBCL. The proposed nomogram supports the clinical impact of cachexia on survival and may contribute to individualized therapy in DLBCL.

Keywords Lymphoma, large B-cell, diffuse · Cachexia · Nutrition assessment · Sarcopenia · Serum albumin · Lymphocyte count

Introduction

Cachexia is an indicator of tumor progression in patients with malignancy [1]. Cachectic patients exhibit intolerance and a reduced response to antitumor therapy, and have an unfavorable prognosis [2–4]. An international consensus proposed

diagnostic criteria for cancer cachexia including weight loss, low body mass index (BMI), and/or presence of sarcopenia [5]. Other potential biomarkers (e.g., albumin, C-reactive protein, pro-inflammatory cytokines, and microRNAs) [6–8] and scoring systems (e.g., cachexia score [CASCO], Glasgow prognostic score [GPS], prognostic nutritional index [PNI]) [9–11] have also been studied to diagnose cancer cachexia and assess its severity.

Diffuse large B cell lymphoma (DLBCL) is a subtype of aggressive non-Hodgkin's lymphoma (NHL) accounting for 32.5% of NHL cases [12]. Although many novel therapeutic agents have been actively developed, treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remains the standard first-line therapy for DLBCL [13, 14]. The International Prognostic Index (IPI) and its variants are widely used to determine the prognosis of DLBCL patients [15, 16]. Several biomarkers and scoring systems associated with cancer cachexia have also been evaluated in patients with DLBCL in the rituximab era. Hypoalbuminemia and elevated CRP levels are associated

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with worse survival [17–19]. Overweight or obese patients experience less treatment-related complications and improved survival in Western countries [20–22], whereas the opposite observations or inconsistent findings between sexes have been reported in Asian patients [23, 24]. Sarcopenia, as determined using computed tomography (CT), is associated with an increased risk for treatment-related complications, frequent treatment discontinuation, and worse survival [25–28]. The PNI, which was originally designed to evaluate the risk for postoperative complications after gastrointestinal surgery [11], has also been evaluated in patients with DLBCL. Zhou et al. reported that a low PNI was an independent prognostic factor for event-free and overall survival (OS) [29].

In this study, we assessed the associations among PNI, other clinical outcomes, and survival in patients with DLBCL. Then we sought valid cachexia markers with prognostic significance and designed a novel model to improve the prognostic ability of well-known clinical indices for patients with DLBCL.

Methods

Patients

We retrospectively identified all consecutive DLBCL patients treated with first-line R-CHOP immunochemotherapy between January 2004 and February 2017 at a single institution. Those for whom pretreatment laboratory parameters, BMI, and CT scans covering the thorax and abdomen were available were included in the analysis. Patients who had histological transformation to DLBCL, active infection at the beginning of R-CHOP therapy, and missing values for IPI were excluded. The Institutional Review Board of Gyeongsang National University Hospital approved this study.

Measurements and definitions

Pretreatment clinical information including demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), B-symptoms, maximum tumor size, cell of origin determined by the Hans algorithm [30], laboratory parameters, and CT scans were reviewed. Hypoalbuminemia was defined as serum albumin < 3.5 g/dL. BMI was calculated as the weight in kilograms divided by the height in square meters (kg/m^2). Being overweight was defined according to Asian ($\text{BMI} \geq 23.0 \text{ kg}/\text{m}^2$) or Western standards ($\text{BMI} \geq 25.0 \text{ kg}/\text{m}^2$) [20, 31]. PNI was calculated as $10 \times \text{serum levels of albumin (g/dL)} + 0.005 \times \text{absolute lymphocyte count } (/\text{mm}^3)$. Patients with a PNI < 40 were categorized as the low-PNI group [11]. The treatment response was assessed using the revised International Working Group response criteria [32]. Treatment-related toxicity was evaluated according to the

National Cancer Institute Common Toxicity Criteria (version 4.0). Treatment discontinuation occurred if the planned treatment schedule (6–8 cycles of R-CHOP for localized or advanced disease or 3–4 cycles of R-CHOP with involved-field radiotherapy for localized disease) was not completed. Treatment-related mortality was defined as death caused directly by treatment at any time or from any cause other than disease progression within 1 month of the last cycle of R-CHOP.

Muscle mass measurement

The detailed method used to measure muscle mass is described elsewhere [27]. Briefly, a radiologist with 9 years of experience measured the mass of the pectoralis major and minor muscles (PM) and the muscle mass of the third lumbar vertebra level including the psoas, abdominal wall, and paraspinal muscles (L3). Reconstructed axial images with a 3-mm slice thickness and interval were analyzed using CT histogram software (the “X section” analysis tool of Advantage Window 4.4; GE Healthcare, Milwaukee, WI, USA). Using freehand manual drawing, the region of interest was placed at the outermost border of muscles. Then, muscles ranging from –29 to 100 HU were measured as the cross-sectional area (cm^2) using CT histogram analysis. The bilateral masses of the PM were measured separately and averaged. The skeletal muscle index (SMI) was calculated by dividing the cross-sectional area of the muscles by height in meters squared (cm^2/m^2); it was categorized as PM-SMI and L3-SMI according to the region of measurement. Sarcopenia was defined as an SMI of less than the cut-off value for SMI, as reported previously (cut-off value for PM-SMI, $4.4 \text{ cm}^2/\text{m}^2$ in males and $3.1 \text{ cm}^2/\text{m}^2$ in females; cut-off value for L3-SMI, $52.4 \text{ cm}^2/\text{m}^2$ in males and $38.5 \text{ cm}^2/\text{m}^2$ in females) [27, 33]. We previously reported that more prognostic information could be obtained when the L3- and PM-SMIs were used together to define sarcopenia [27]. Therefore, the degree of sarcopenia was categorized as follows: sarcopenia-both, both L3- and PM-SMIs are at sarcopenic levels; sarcopenia-L3/PM alone, only one SMI is at a sarcopenic level; non-sarcopenia-both, neither SMI is at a sarcopenic level.

Statistical analysis

A value of $p < 0.05$ was considered statistically significant. Chi-square or Fisher’s exact tests and Mann-Whitney U -tests were used to analyze the relationship between PNI and categorical variables and continuous variables, respectively. Pearson’s correlation coefficient was used to test the correlations among continuous variables.

For survival analysis, progression-free survival (PFS) was defined as the time from the start of R-CHOP therapy to first progression, death from any cause, or last follow-up. OS was

defined the same as the time from the start of R-CHOP therapy to death from any cause or last follow-up. Kaplan-Meier curves were plotted and compared using log-rank tests for

survival data. Cox regression analyses were performed to identify independent prognostic factors. The final prognostic model was determined using the backward selection method

Table 1 Patients' characteristics and treatment response

Factor	PNI < 40 (<i>n</i> = 69)	PNI ≥ 40 (<i>n</i> = 159)	<i>p</i>
Median age (range), years	71 (39–88)	60 (21–86)	< 0.001
Sex			0.206
Male	35 (50.7)	95 (59.8)	
Female	34 (49.3)	64 (40.3)	
ECOG PS			< 0.001
0–1	36 (52.2)	128 (80.5)	
2–3	33 (47.8)	31 (19.5)	
B-symptoms			0.002
Absent	47 (68.1)	137 (86.2)	
Present	22 (31.9)	22 (13.8)	
Bulky disease			0.018
Non-bulky	51 (73.9)	138 (86.8)	
Bulky	18 (26.1)	21 (13.2)	
Ann Arbor stage			0.003
I–II	20 (29.0)	80 (50.3)	
III–IV	49 (71.0)	79 (49.7)	
Extranodal disease			0.002
Absent	35 (50.7)	115 (72.3)	
Present	34 (49.3)	44 (27.7)	
LDH			< 0.001
Normal	11 (15.9)	81 (50.9)	
Elevated	58 (81.1)	78 (49.1)	
IPI			< 0.001
Low	10 (14.5)	65 (40.9)	
Low-intermediate	11 (15.9)	40 (25.2)	
High-intermediate	16 (23.2)	26 (16.4)	
High	32 (46.4)	28 (17.6)	
Cell of origin (<i>n</i> = 135)			0.065
GCB	12 (28.6)	14 (15.1)	
Non-GCB	30 (71.4)	79 (85.0)	
Median PM-SMI (range), cm ² /m ²	4.2 (2.0–8.5)	4.7 (1.9–10.5)	0.007
Median L3-SMI (range), cm ² /m ²	47.8 (27.8–70.8)	52.2 (31.7–90.9)	0.001
Median albumin (range), g/dL	3.6 (2.7–4.1)	4.2 (2.6–4.8)	< 0.001
Median BMI (range), kg/m ²	22.6 (15.6–30.4)	23.3 (15.1–33.7)	0.049
Treatment response (<i>n</i> = 211)*			< 0.001
CR	35 (60.3)	134 (87.6)	
PR, NR/SD, or PD	23 (39.7)	19 (12.4)	

Data are presented as number of patients (%) except age

PNI prognostic nutritional index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *IPI* International Prognostic Index, *GCB* germinal center B cell, *PM-SMI* pectoralis muscle skeletal muscle index, *L3-SMI* L3 skeletal muscle index, *BMI* body mass index, *CR* complete response, *PR* partial response, *NR* no response, *SD* stable disease, *PD* progressive disease

*Information for treatment response was not available in 17 patients due to the following reasons: early discontinuation of treatment due to treatment toxicity after the first cycle of chemotherapy (*n* = 8), patient's own will to withdraw the treatment (*n* = 5), early transfer to another hospital (*n* = 2), and early loss of follow-up (*n* = 2)

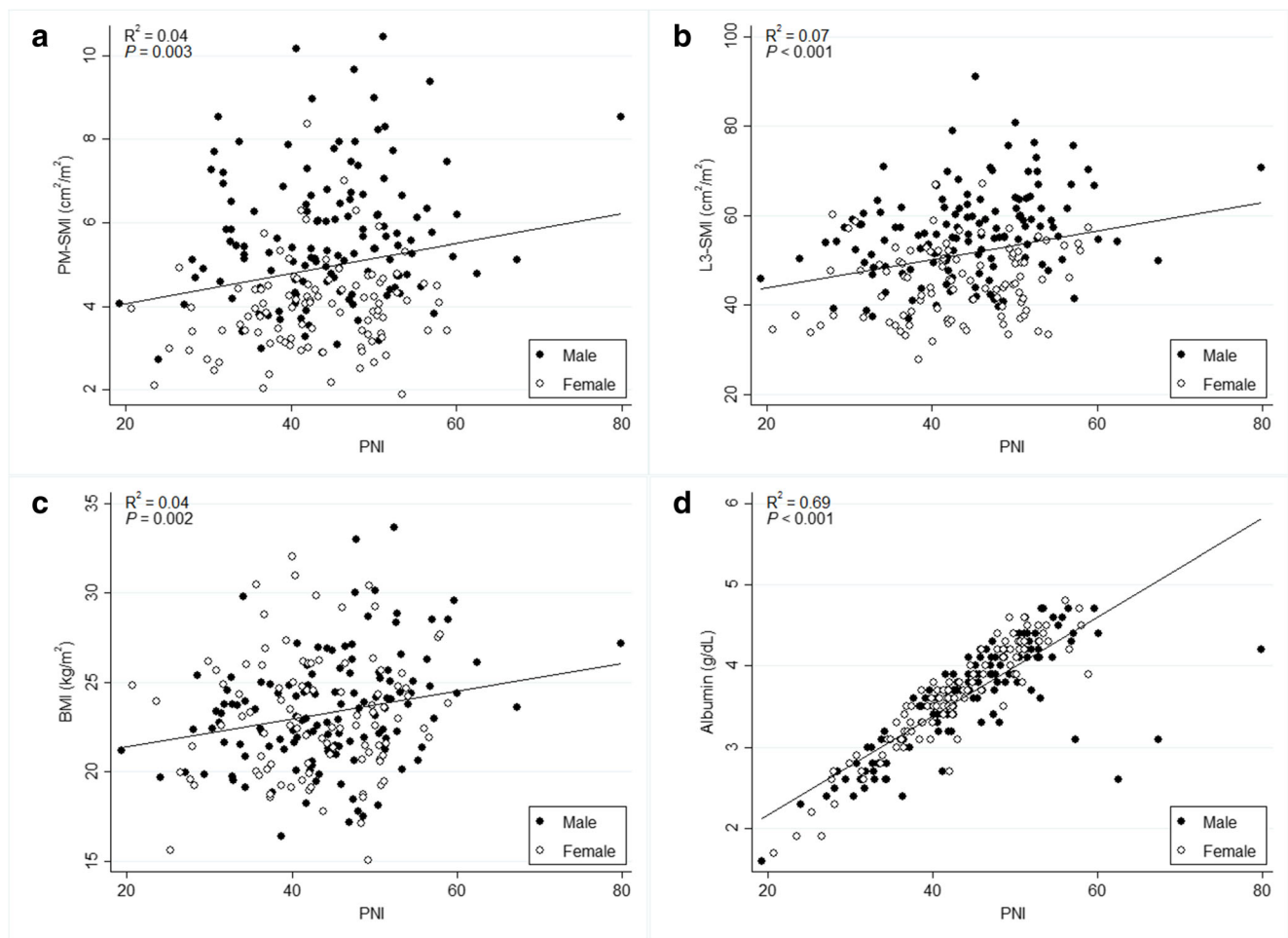


Fig. 1 Linear regression between PNI and PM-SMI (**a**), L3-SMI (**b**), BMI (**c**), and serum albumin (**d**) level. *PNI* prognostic nutritional index, *PM-SMI* pectoralis muscle skeletal muscle index, *L3-SMI* L3 skeletal muscle index, *BMI* body mass index

for potentially significant variables ($p < 0.10$) in univariate analyses.

The nomogram, a simple graphical representation of a statistical predictive model [34], was constructed from the final Cox regression model to predict the 3- and 5-year OS rates of

each individual patient. Briefly, each point obtained from the covariates of the final Cox regression model is summed to total point, which is converted to the probability of the 3- and 5-year survival of a patient. The concordance index (c-index) was calculated to test the discriminatory ability of the

Table 2 Treatment-related toxicity

	PNI < 40 ($n = 69$)	PNI \geq 40 ($n = 159$)	p
Hematologic toxicity, grade \geq 3			
Anemia	19 (27.5)	26 (16.4)	0.051
Neutropenia	63 (91.3)	124 (78.0)	0.016
Thrombocytopenia	30 (43.5)	30 (18.9)	< 0.001
Febrile neutropenia	37 (53.6)	35 (22.0)	< 0.001
Any non-hematologic toxicity, grade \geq 3	32 (46.4)	51 (32.1)	0.039
Treatment-related mortality	11 (15.9)	9 (5.7)	0.012
Treatment discontinuation*	30 (43.5)	14 (8.8)	< 0.001

PNI prognostic nutritional index

*Four patients discontinued the treatment due to early disease progression

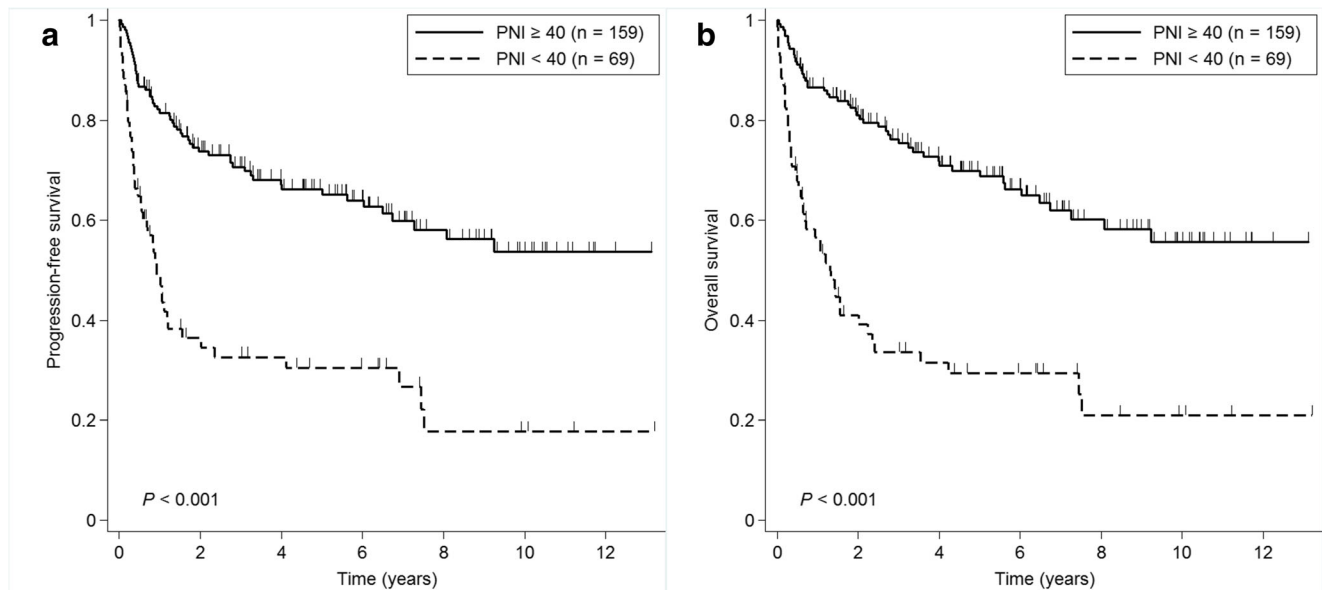


Fig. 2 Kaplan-Meier curves of PFS (**a**) and OS (**b**) according to PNI. *PFS* progression-free survival, *OS* overall survival, *PNI* prognostic nutritional index

nomogram. The higher the c-index, the greater the ability of the model to predict the outcome. A c-index of 0.5 indicates that a model predicts no better than a chance, whereas a c-index of 1.0 means perfect predictability. The bias-corrected c-index was also calculated using 200 bootstrap resamplings to estimate the optimism of the final model (internal validation). A calibration plot was created to compare the predicted probability from the nomogram to the actual probability. R software using the “rms” package (ver. 3.4.0; R Foundation for Statistical Computing, Vienna, Austria) was used to construct the nomogram and calibration plot. All other statistical analyses were performed using Stata software (ver. 14.0; Stata Corp., College Station, TX, USA).

Results

Patient characteristics

A total of 228 patients were included and assigned to the low- ($n = 69$) or high- ($n = 159$)-PNI groups. The median age was 64 years (range, 21–88 years) and 130 patients (57.0%) were male. Most patients had a good ECOG PS (0–1, 71.9%). A total of 9.2%, 34.7%, 21.9%, and 34.2% patients had low, low-intermediate, high-intermediate, and high IPI scores, respectively. Germinal center B cell-like DLBCL was reported in 26 of 135 available patients (19.3%).

Table 1 shows the differences in patient characteristics between the low- and high-PNI groups. Low PNI was generally associated with adverse clinical factors such as old age, poor PS, an increased incidence of B-symptoms, bulky disease, extranodal involvement, more advanced stage, higher serum

levels of LDH, and IPI score. There were no statistically significant differences in sex and the cell of origin.

Association between PNI and other nutritional factors

The correlations between PNI and other nutritional factors such as PM-SMI, L3-SMI, albumin, and BMI were analyzed. When the nutritional factors were assessed as continuous variables, there were weak but significant positive associations between PNI and PM-SMI ($R^2 = 0.04$, $p = 0.003$; Fig. 1a), L3-SMI ($R^2 = 0.07$, $p < 0.001$; Fig. 1b), and BMI ($R^2 = 0.04$, $p = 0.002$; Fig. 1c). Serum albumin, a component of PNI, was strongly associated with PNI ($R^2 = 0.69$, $p < 0.001$; Fig. 1d). Similar findings were observed when PNI was assessed as a dichotomized variable. The low-PNI group had lower PM- and L3-SMIs, serum levels of albumin, and BMI compared to the high-PNI group (Table 1).

Treatment response and toxicity

Information regarding the treatment response was available for 211 of the 228 patients. The complete response (CR) rate was lower in the low-PNI group than in the high-PNI group (60.3% vs. 87.6%, respectively; $p < 0.001$; Table 1). When 24 of the 211 available patients who prematurely discontinued treatment for reasons other than disease progression were excluded from the analysis, the CR rate remained lower in the low-PNI group than the high-PNI group (75.6% vs. 90.4%, $p = 0.012$).

Data regarding treatment-related toxicity and compliance with treatment were available for all 228 patients (Table 2). The incidence of grade ≥ 3 neutropenia (91.3% vs. 78.0%),

Table 3 Cox regression for PFS and OS

Factor	PFS				OS						
	Univariate		Multivariate		Univariate		Multivariate				
	HR	95% CI	<i>p</i>	95% CI	HR	95% CI	<i>p</i>	95% CI			
PNI (< 40 vs. ≥ 40)	3.104	2.101–4.587	< 0.001	1.344–3.059	0.001	3.390	2.267–5.070	< 0.001	1.423–3.329	< 0.001	
Sarcopenia											
None	Ref.			Ref.		Ref.			Ref.		
Intermediate	1.899	1.232–2.927	0.004	1.025–2.478	0.039	2.141	1.367–3.353	0.001	1.805	1.139–2.861	0.012
Both	5.278	3.122–8.920	< 0.001	1.944–5.740	< 0.001	5.803	3.364–10.007	< 0.001	3.691	2.098–6.494	< 0.001
Albumin (< 3.5 g/dL vs. ≥ 3.5 g/dL)	3.571	2.417–5.278	< 0.001			3.877	2.584–5.816	< 0.001			
ALC* (≥ 1325/mm ³ vs. < 1325 mm ³)	1.515	0.984–2.333	0.059			1.591	1.022–2.476	0.040			
BMI (< 25 kg/m ² vs. ≥ 25 kg/m ²)	1.464	0.906–2.365	0.119			1.651	0.989–2.756	0.055			
BMI (< 23 kg/m ² vs. ≥ 23 kg/m ²)	1.016	0.691–1.494	0.935			1.096	0.735–1.632	0.653			
IPI											
Low	Ref.			Ref.		Ref.			Ref.		
Low-intermediate	3.716	1.808–7.638	< 0.001	1.716–7.300	0.001	3.104	1.479–6.517	0.003	2.945	1.398–6.202	0.004
High-intermediate	5.938	2.883–12.231	< 0.001	2.477–10.757	< 0.001	4.801	2.290–10.063	< 0.001	4.177	1.970–8.856	< 0.001
High	16.373	8.253–32.480	< 0.001	5.650–23.212	< 0.001	16.639	8.312–33.309	< 0.001	11.312	5.524–23.162	< 0.001
Other clinical variables											
Sex (male vs. female)	1.121	0.757–1.659	0.569			1.109	0.739–1.664	0.619			
B-symptoms (present vs. absent)	2.574	1.694–3.913	< 0.001			2.372	1.533–3.671	< 0.001			
Bulky disease (bulky vs. non-bulky)	0.874	0.513–1.490	0.621			0.810	0.459–1.428	0.466			

PFS progression-free survival, OS overall survival, HR hazard ratio, CI confidence interval, PNI prognostic nutritional index, ALC absolute lymphocyte count, BMI body mass index, IPI International Prognostic Index

*Stratified by the median value

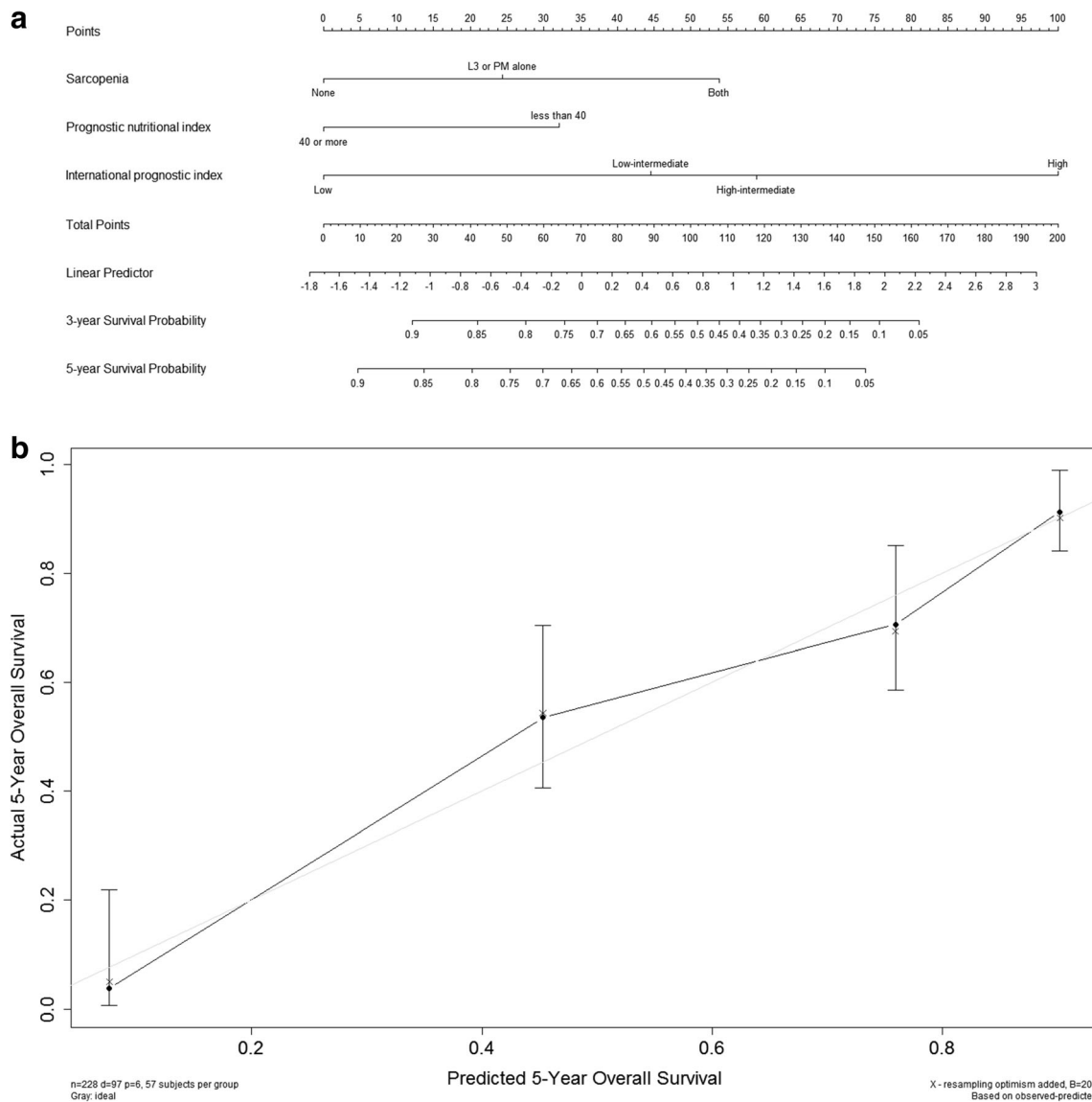


Fig. 3 **a** Nomogram to predict the 3- and 5-year OS rates in DLBCL patients receiving first-line R-CHOP immunochemotherapy. **b** Calibration plot of the nomogram for the 5-year OS adjusted by

bootstrapping with 200 resamples. OS overall survival, DLBCL diffuse large B cell lymphoma, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

thrombocytopenia (43.5% vs. 18.9%), febrile neutropenia (53.6% vs. 22.0%), and any non-hematological toxicities (46.4% vs. 32.1%) was significantly higher in the low-PNI group than the high-PNI group. Treatment-related mortality (15.9% vs. 5.7%) and treatment discontinuation (43.5% vs. 8.8%) were also more common in the low-PNI group than the high-PNI group.

Survival

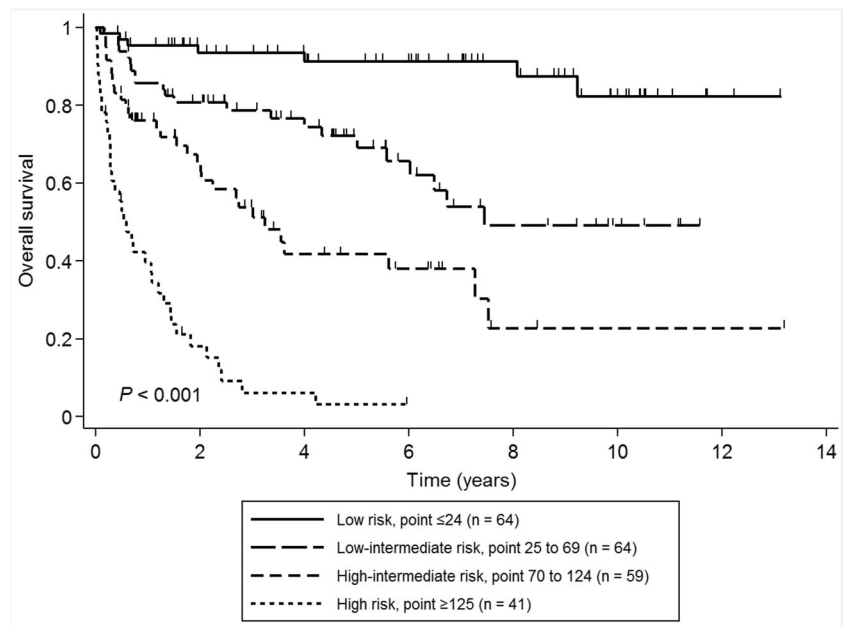
At the time of analysis, 46 (66.7%) and 51 (32.1%) patients experienced death in the low- and high-PNI groups, respectively. After a median follow-up duration of 76 months for the low-PNI group and 69 months for the high-PNI group, the estimated median PFS was

11.2 months (95% CI, 6.6 to 18.6 months) in the low-PNI group and was not reached (95% CI, 87.2 months to NR) in the high-PNI group ($p < 0.001$; Fig. 2a). The estimated median OS was 15.6 months (95% CI, 7.7 to 26.9 months) in the low-PNI group and was not reached (95% CI, 87.2 months to NR) in the high-PNI group ($p < 0.001$; Fig. 2b). In multivariate analyses, low PNI, sarcopenia, and higher IPI score were independent prognostic factors for poor PFS and OS (Table 3).

Nomogram predicting survival

A nomogram was constructed to predict patient survival using the final Cox model for OS (Fig. 3a). The nomogram showed excellent discrimination for predicting OS

Fig. 4 Kaplan-Meier curves of OS according to the nomogram score. OS overall survival



(original c-index, 0.80; bias-corrected c-index, 0.79) compared to the IPI alone (original c-index, 0.75). The calibration plot of the nomogram exhibited good concordance between the predicted and actual probabilities for 5-year OS (Fig. 3b).

Based on the survival probabilities predicted by the nomogram, the patients were stratified into four risk groups as follows: low (total points ≤ 24), low-intermediate (25–69), high-intermediate (70–124), and high (≥ 125) (Fig. 4). The estimated median OS according to the nomogram-based risk model was not reached, 89.4, 38.8, and 7.0 months in the low, low-intermediate, high-intermediate, and high-risk groups, respectively ($p < 0.001$).

Discussion

We found that PNI can be a prognostic factor in patients treated with first-line R-CHOP therapy for DLBCL. Patients with low PNI were at 118% higher risk for death and had a 28% lower rate of CR compared to those with high PNI, consistent with previous results (134% higher risk for death and 23% lower rate of CR) [29]. In addition to the findings in the previous study, we newly found that the low-PNI group showed more frequent treatment-related toxicities and mortality and early withdrawal from treatment, which may result in a low CR rate and poor survival.

As described above, PNI consists of serum levels of albumin and absolute lymphocyte count (ALC). There is evidence that each factor is associated with the prognosis of DLBCL patients. The 5-year OS rates of patients with a high NCCN-IPI and hypoalbuminemia and normal albumin level were

29.2% and 60%, respectively [17]. The combined use of serum levels of albumin and platelet count may more accurately predict survival in patients with DLBCL [35]. Recently, a Chinese study proposed the Age, Comorbidities, and Albumin (ACA) index as a part of an effective comprehensive geriatric assessment tool for elderly DLBCL patients. In that study, the moderate to poor ACA group had a higher 2-year treatment-related mortality rate and poorer survival rate compared to the excellent to good ACA group [36]. The clinical role of ALC in patients with DLBCL has also been studied. A meta-analysis covering 1206 DLBCL patients reported that the summarized hazard ratio of low ALC for OS is 2.78 (95% CI, 1.87–4.13, $p < 0.001$) in those treated with R-CHOP [37]. The combined use of ALC and serum-free light chains is useful for the prognostic stratification of DLBCL [38]. A recent prospective study developed the IPI24 model, consisting of bulky disease, ECOG PS, serum levels of LDH, tumor stage, sex, age, and ALC, which had superior discriminatory ability (c-index, 0.67) compared to IPI or NCCN-IPI [39]. As such, because each parameter of PNI is associated with prognosis, PNI is an appropriate prognostic factor in patients with DLBCL, as shown in the present study.

In the current study, the PNI showed the possibility of easily available biomarker for cancer cachexia, given that there were positive correlations between PNI and other biomarkers for cancer cachexia such as SMI, BMI, and serum levels of albumin (Fig. 1). The high frequency of treatment-related toxicities and early treatment discontinuation observed in the low-PNI group may be explained by cancer cachexia. In most clinical practice, chemotherapy dose is determined by body surface area which does not directly reflect muscle mass. It may increase the risk of dose-limiting toxicity, especially in

the patients with sarcopenic obesity [40]. There are several clinical evidences supporting the association between cancer cachexia and treatment-related toxicity in cancer patients treated with anthracycline-containing chemotherapy [26, 41, 42]. Considering our findings and previous studies, we suggest that dose reduction of R-CHOP with intensive supportive care should be considered to overcome the poor prognosis of the low-PNI group, rather than the use of more intensified treatment regimen.

In a previous study, the prognostic significance of IPI was not independent when adjusted for PNI on multivariate analysis in DLBCL [29]. Another novel finding of the present study is that the prognostic impact of PNI was significant together with the presence of sarcopenia (a diagnostic criterion for cancer cachexia) and the IPI in DLBCL. Based on this finding, we could develop a new nomogram-based prognostic model for DLBCL that included IPI, sarcopenia, and PNI. The discriminatory ability of the nomogram to predict the survival was more favorable compared to that of the IPI alone (c-index 0.80 vs. 0.75, respectively). This model suggests that cachexia may provide additional prognostic information when combined with the IPI in patients with DLBCL.

The main limitation of this study is inherent to its retrospective nature. While objective data such as laboratory values, skeletal muscle index, and hematological toxicity were accurately analyzed, subjective data including B-symptoms and non-hematological toxicity might be underestimated because this information depended on past medical records written by physicians before the study was planned. The time interval for evaluating the treatment response and relapse was not uniform according to each patient's clinical status and the physician's usual practice. To minimize the bias caused by these features, we limited the inclusion criteria to patients treated with only an R-CHOP regimen as the first-line chemotherapy at a single institution. The relatively small sample size was another limitation. However, the number of patients ($n = 228$) treated with R-CHOP was higher than that in a previous study ($n = 151$) that evaluated the association between the PNI and DLBCL [29]. Finally, the true clinical implications of the PNI according to the cell of origin remain to be determined due to many missing data and retrospective nature of this study.

In conclusion, this study supports the results of a previous study [29], whereby low PNI is an independent poor prognostic factor in patients with DLBCL treated with first-line R-CHOP immunochemotherapy. In addition, we newly found that treatment-related toxicity and early discontinuation of treatment occurred more frequently in DLBCL patients with low PNI. We anticipate that the new prognostic nomogram developed using PNI, SMI, and IPI may help to realize individualized therapy that considers both the disease characteristics and the patient's tolerance to treatment in patients with DLBCL. This will be validated externally in a future study.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study is a retrospective analysis without any intervention and thus did not require informed consent.

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