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Relevance of prognostic index with β2-microglobulin for patients with diffuse large B-cell lymphoma in the rituximab era

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Background
The International Prognostic Index (IPI) has been a useful tool for predicting the prognosis of aggressive non-Hodgkin lymphoma in the last 20 years. Herein, we aimed to develop a new prognostic model for diffuse large B-cell lymphoma (DLBCL) in the rituximab era.

Methods
Between March 2004 and June 2012, patients with DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy regimen were identified in the database of the Asan Medical Center (AMC) Lymphoma Registry. The primary and secondary endpoints were a new prognostic index for DLBCL and validation of the National Comprehensive Cancer Network-International Prognostic Index in our cohort, respectively.

Results
The AMC cohort comprised 621 patients. The median follow-up duration was 43.3 months (range, 6.2–122.5 mo). Univariate analysis revealed that age (≤60 vs. >60 yr), lactate dehydrogenase (LDH; within normal vs. increased), Eastern Cooperative Oncology Group performance status (ECOG PS; 0 or 1 vs. ≥2), advanced stage (Ann Arbor stage I/II vs. III/IV), extra-nodal involvement (≤1 vs. >1), B symptoms (no vs. yes), and beta-2 microglobulin (β2MG, ≤2.5 vs. >2.5) can be used to predict overall survival (OS). In multivariate analysis, only age, LDH, ECOG performance status, and β2MG were significantly associated with OS, and we developed a new prognostic model with these 4 factors. The new prognostic model showed better discriminative power compared with the classic IPI.

Conclusion
Our new prognostic index model for DLBCL in the rituximab era has good discriminative power and is convenient to use.

Key Words Diffuse large B-cell lymphoma, Prognostic index, NCCN-IPI, β2-microglobulin

INTRODUCTION

The prognosis of diffuse large B-cell lymphoma (DLBCL) has been notably improved since rituximab was introduced for standard therapeutic strategy in the early 2000s [1-5]. The incorporation of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy (i.e., R-CHOP) yielded 15% absolute overall survival (OS) benefit. However, approximately 40% of patients with DLBCL still die of relapsed or refractory disease. To improve the survival outcomes of patients with DLBCL, patients with high risk of relapse and death should be identified.

The International Prognostic Index (IPI) was proposed in 1993, before the introduction of rituximab, and demonstrated more predictive prognostic power than the Ann Arbor staging system [6]. The IPI classifies patients into 4 risk groups for survival using age, serum level of lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group performance status (ECOG PS), Ann Arbor stage, and the number of extranodal involvement site. However, since rituximab improved survival outcomes throughout the risk

groups, the discriminative role of IPI in the rituximab era has been questioned. Three large prospective phase II/III trials evaluated the IPI and revealed its validity in the rituximab era [7]. Sehn *et al.* [8] also demonstrated the validity of the original IPI and proposed a revised IPI by redistributing patients into three prognostic groups using the IPI factors. While the original IPI was shown to be valid in the rituximab era, the OS in the high-risk group was above 50%. Therefore, several attempts have been made to develop and validate models with better predictive and discriminative capabilities in the rituximab era. Since the inclusion of molecular analysis in the classification of lymphoma, gene expression profile and molecular prognostic factors contributed to generate a molecular portrait of distinct types of B-cell lymphoma [9, 10]. However, the analysis of the results of gene expression profiling and immunohistochemical staining has practical limitations in terms of clinical availability and technical standardization. Recently, the National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI), which is an enhanced IPI using fractionation of age and LDH, was reported to have better discriminative function between low- and high-risk than the original IPI [11]. Although the NCCN-IPI demonstrated enhanced discriminative capability compared to the original IPI, its application may be limited in clinical practice because of its multiple categorized scoring system.

Beta-2 microglobulin (β2MG) is a non-glycosylated protein consisting of a small invariable light chain subunit of a major histocompatibility complex class I antigen [12]. Increased serum β2MG level in patients with non-Hodgkin lymphoma has been suggested to correlate with poor prognosis [13-15]. The serum level of β2MG has also been shown to have prognostic implications in association with the original IPI as well as NCCN-IPI in DLBCL [16, 17]. Hence, we aimed to explore the prognostic model with serum β2MG, which not only has relevant discriminative power, but is also convenient for clinical use.

MATERIALS AND METHODS

Between March 2004 and June 2012, 692 patients with de novo DLBCL treated with R-CHOP were identified in the database of the Asan Lymphoma Registry, Asan Medical

Table 1. Baseline characteristics of the patients in AMC and PROCESS cohorts.

Characteristics	AMC cohort		PROCESS cohort		*P*
	N=621	%	N=434	%	
Age, yr					
Median (range)	57 (16–85)		60 (20–89)		0.001
≤60	377	60.7	227	52.3	0.008
>60	244	39.3	207	47.7	
Gender					0.614
Male	343	55.2	247	56.9	
Female	278	44.8	187	43.1	
Serum lactate dehydrogenase levels					0.234
Normal	334	53.8	217	50.0	
Elevated	287	46.2	217	50.0	
ECOG PS					0.047
0 or 1	569	91.6	381	87.8	
≥2	52	8.4	53	12.2	
Ann Arbor stage					0.453
I and II	293	47.2	215	49.5	
III and IV	328	52.8	219	50.5	
Number of extranodal involvement					0.744
<2	403	64.9	277	63.8	
≥2	218	35.1	157	36.2	
B symptoms					<0.001
No	549	88.4	324	74.7	
Yes	72	11.6	110	25.3	
International Prognostic Index					0.744
Low/low-intermediate	404	65.1	278	64.1	
High-intermediate/high	217	34.9	156	35.9	
Beta-2 microglobulin, mg/L					
Median (range)	2.1 (0.95–66.00)		2.1 (0.45–38.81)		0.889
≤2.5	422	68.0	285	65.7	0.464
>2.5	199	32.0	149	34.3	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Center (AMC), Seoul, Korea. This study was approved by the Asan Medical Center Institutional Review Board.

The patients' baseline characteristics including age, gender, Ann Arbor stage (I–IV), the number and specific sites of extranodal involvement, serum LDH level, serum level of β2MG, ECOG PS (0–4), presence of bulky disease (>10 cm), and B symptoms (defined as recurrent fever, night sweats, or >10% weight loss) were collected prospectively. After completion of chemotherapy, patients who achieved complete response were followed up every three months for the first two years, every six months for the next three years, and annually thereafter. Relapse-free survival (RFS) was defined as the time between diagnosis to relapse or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to death from any cause.

In the current study, we validated our prognostic index model in Prospective Cohort Study with Central Nervous System Evaluation in Diffuse Large B-cell Lymphoma (PROCESS) cohort, which collected data from 27 centers in Korea since August 2010 (NCT01202448). PROCESS was designed to evaluate the incidence of central nervous system (CNS) relapse or involvement in patients with DLBCL. Eligible patients were those aged 20 years or older, had newly diagnosed DLBCL, and had a life expectancy of more than 6 months. Patients were excluded if they had primary CNS lymphoma.

We used the Kaplan-Meier method and log-rank test to analyze RFS and OS and to compare the two survival distributions, respectively. We estimated the hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) using the Cox proportional hazards regression model. Model discrimination was assessed by calculating the area under the receiver-operator-characteristic (ROC) curve (AUC), and concordance index (C-index)was used to calculate the overall death rate 5 years after diagnosis. A C-index of 0.5 represents no predictive discrimination, while an index of 1 represents perfect ability to distinguish patients. External validation was estimated via calibration slope. Independent PROCESS dataset was used to validate the prognostic model. All statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Among the 692 patients in AMC DLBCL cohort, 621 (89.7%) had complete clinical information, whereas 434 (71.9%) out of the 604 patients in PROCESS cohort had complete clinical information. The baseline characteristics are described in Table 1. The median age of the patients in AMC and PROCESS cohort was 57 years (range, 16–85) and 60 years (range, 20–89), respectively. AMC and PROCESS cohort comprised 55% and 56.9% of men, respectively. The median level of β2MG were 2.1 mg/L (range, 1.0–66.0) and 2.1 mg/L (range, 0.45–38.81) in AMC and PROCESS cohort, respectively. Ann Arbor stage, serum LDH, number of extranodal involvement, and IPI status were comparable in both cohorts. However, patients in PROCESS cohort were older and had worse ECOG PS and more B symptoms than those in AMC cohort.

Table 2. Univariate analysis of clinical prognostic factors for overall survival.

Factors	HR	95% CI	*P*
Age, yr			<0.001
≤60	1	2.068–4.118	
>60	2.918		
Serum lactate dehydrogenase levels			<0.001
Normal	1	2.742–5.964	
Elevated	4.044		
ECOG PS			<0.001
0 or 1	1	2.274–5.359	
3 or 4	3.491		
Ann Arbor stage			<0.001
I and II	1	1.965–4.213	
III and IV	2.877		
Number of extranodal sites			<0.001
<2	1	1.615–3.172	
≥2	2.263		
Extranodal disease[a]			0.363
No	1	0.835–1.638	
Yes	1.169		
Presence of B symptoms			0.071
No	1	1.103–2.757	
Yes	1.743		
Beta-2 microglobulin, mg/L			<0.001
≤2.5	1	2.173–4.272	
>2.5	3.046		

[a]Lymphomatous involvement in bone marrow, CNS, liver/GI tract, or lung.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 3. Clinical prognostic factors of 5-year overall survival from multivariate analysis in AMC cohort.

Factors	HR	95% CI	*P*	Score
Age, yr			<0.001	
≤60	1	1.566–3.221		0
>60	2.246			1
Serum lactate dehydrogenase levels			<0.001	
Normal	1	1.712–4.095		0
Elevated	2.648			1
ECOG PS			0.017	
0 or 1	1	1.102–2.712		0
3 or 4	1.728			1
Ann Arbor stage			0.108	
I and II	1	0.925–2.193		0
III and IV	1.425			1
Beta-2 microglobulin, mg/L			0.089	
≤2.5	1	0.951–2.042		0
>2.5	1.393			1

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

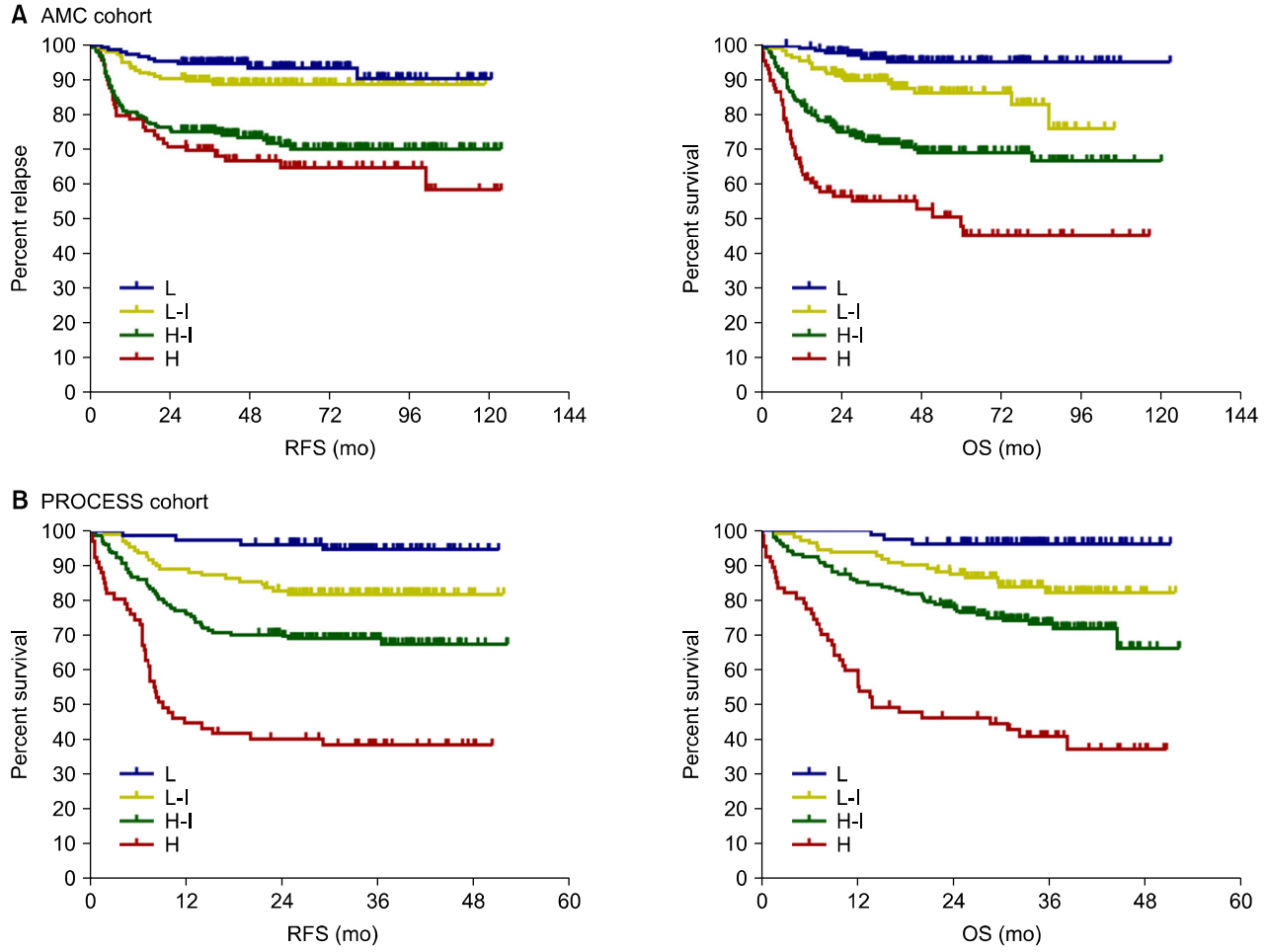

Fig. 1. Overall survival and relapse-free survival of **(A)** AMC cohort and **(B)** PROCESS cohort. Our model was found to have high prognostic capability in the multicenter prospective cohort (PROCESS).
Abbreviations: H, high-risk group; H-I, high-intermediate; L, low; L-I, low-intermediate.

Table 4. Comparison of classic IPI, NCCN-IPI, and modified prognostic model for risk stratification and outcomes of 5-year OS and RFS in AMC and PROCESS cohorts.

	Score			5-yr OS			5-yr RFS		
	Classic IPI	NCCN-IPI	Modified prognostic model	Classic IPI	NCCN-IPI	Modified prognostic model	Classic IPI	NCCN-IPI	Modified prognostic model
AMC cohort (N=621)									
L	0, 1 (48.1%)	0, 1 (20.8%)	0 (23.5%)	88.40%	93.70%	95.20%	90.40%	89.40%	93.30%
L-I	2 (16.9%)	2, 3 (43.8%)	1 (24.6%)	81.20%	81.90%	86.40%	73.90%	84.30%	88.70%
H-I	3 (18.7%)	4, 5 (28.3%)	2, 3 (37.5%)	64.60%	62.50%	69.20%	74.90%	68.10%	71.00%
H	4, 5 (16.3%)	≥6 (7.1%)	4, 5 (14.3%)	44.60%	39.30%	47.80%	59.30%	68.10%	64.80%
PROCESS cohort (N=434)									
L	0, 1 (43.5%)	0, 1 (10.1%)	0 (18.7%)	87.90%	97.70%	96.30%	86.40%	94.60%	94.70%
L-I	2 (20.5%)	2, 3 (43.1%)	1 (25.6%)	77.90%	85.60%	87.40%	74.00%	84.20%	83.80%
H-I	3 (17.7%)	4, 5 (34.8%)	2, 3 (40.3%)	52.20%	59.30%	73.20%	62.30%	62.80%	67.60%
H	4, 5 (18.2%)	≥6 (12.0%)	4, 5 (15.4%)	45.50%	40.10%	37.00%	43.80%	36.50%	38.40%

Abbreviations: H, high-risk group; H-I, high-intermediate; IPI, International Prognostic Index; L, low; L-I, low-intermediate; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index; OS, overall survival; RFS, relapse-free survival.

Univariate analysis showed that age (≤60 vs. >60 yr; HR, 2.918; 95% CI, 2.068–4.118), LDH ratio (≤1 vs. >1; HR, 4.044; 95% CI, 2.742–5.964), ECOG PS (0 or 1 vs. ≥2; HR, 3.491; 95% CI, 2.274–5.359), Ann Arbor stage (1 or 2 vs. 3 or 4; HR, 2.877; 95% CI, 1.965–4.213), number of extranodal involvement site (0 or 1 vs. ≥2; HR, 2.263; 95% CI, 1.615–3.172), and serum β2MG ratio (≤1 vs. >1; HR, 3.046; 95% CI, 2.173–4.272) were significantly associated with OS (Table 2). However, lymphomatous involvement in major organs including the bone marrow (BM), central

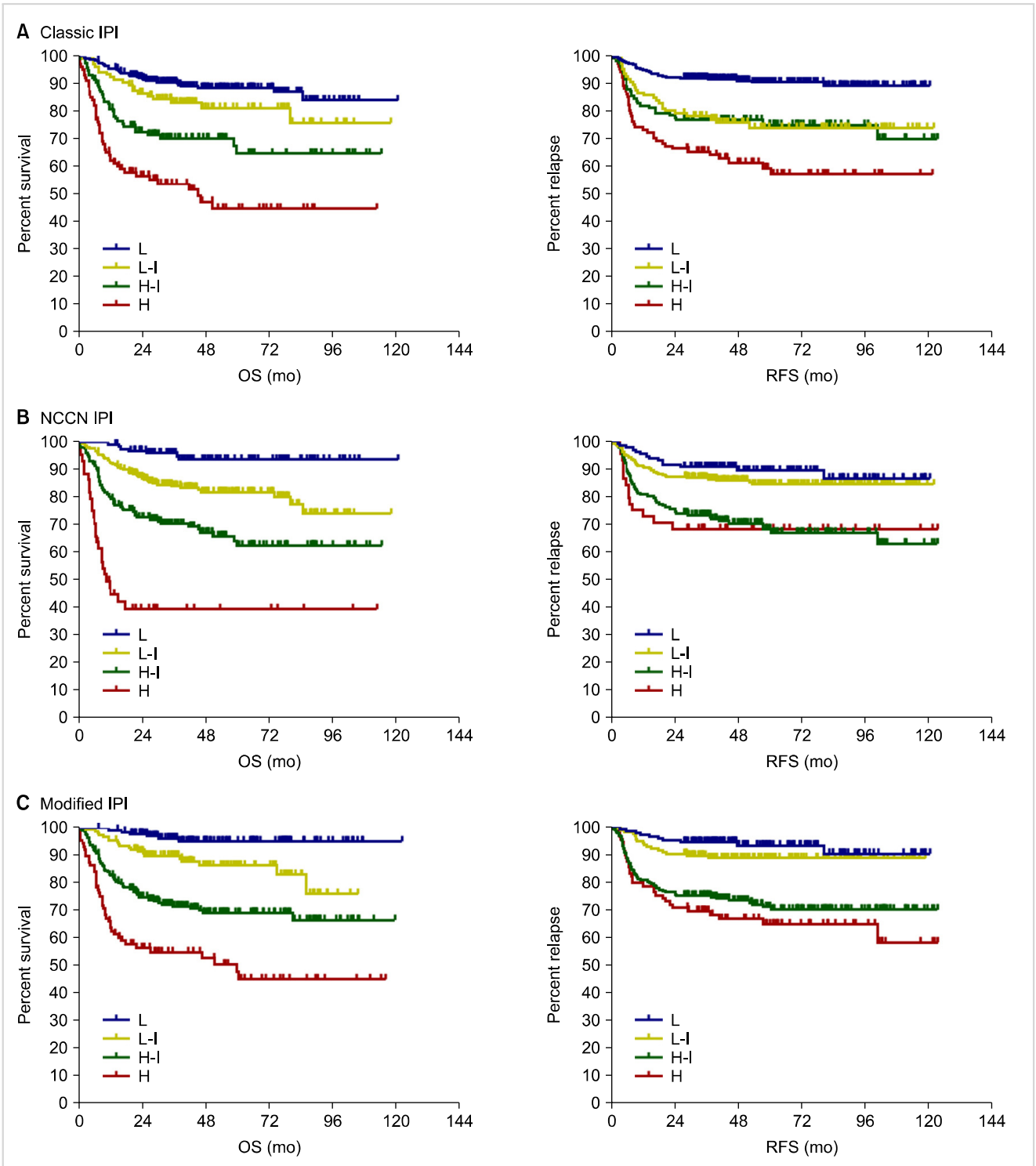

Fig. 2. Overall survival and relapse-free survival according to **(A)** classic IPI, **(B)** NCCN-IPI, and **(C)** modified IPI.
Abbreviations: H, high-risk group; H-I, high-intermediate; IPI, International Prognostic Index; L, low; L-I, low-intermediate; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index; RFS, relapse-free survival.

Table 5. Time-independent AUC and calibration slope in classic IPI, NCCN-IPI, and modified prognostic model.

Prognostic model	Time-independent AUC		Calibration slope		
		95% CI	Point estimator	95% CI	*P*
Classic IPI	0.705	0.659–0.751	0.583	0.484–0.703	<0.001
NCCN-IPI	0.71	0.664–0.757	0.635	0.528–0.764	<0.001
Modified prognostic model	0.739	0.691–0.786	0.75	0.624–0.902	0.002

Abbreviations: AUC, area under the curve; CI, confidence interval; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index.

nervous system, liver/gastrointestinal (GI) tract, or lung did not retain statistical significance in univariate analysis for OS. In addition, individual sites of extranodal involvement were analyzed through univariate analysis. Lymphomatous involvement in the BM, liver, lung, genitourinary tract, and bone showed significant association with OS and RFS. Interestingly, lymphomatous involvement of the GI tract was inversely associated with OS and RFS in AMC cohort (Supplementary Table 1).

Based on the results of univariate analysis of clinical prognostic factors, we established a prognostic model that included age (≤60 vs. >60 yr), serum LDH ratio (ratio ≤1 vs. >1), ECOG PS (0 or 1 vs. ≥2), Ann Arbor stage (1 or 2 vs. 3 or 4), and serum β2MG ratio (ratio ≤1 vs. >1) (Table 3). Although Ann Arbor stage was not significantly associated with OS in multivariate analysis, we included it in the prognostic model because it has been widely accepted as a significant prognostic factor reflecting tumor extent. Each factor corresponded to 1-point score.

According to the prognostic score, 4 risk groups were defined: low (0 point), low-intermediate (1 point), high-intermediate (2–3 points), and high (4–5 points). The five-year OS rates were 95.2%, 86.4%, 69.2%, and 47.8% in the low-, low-intermediate-, high-intermediate-, and high-risk group, respectively (Fig. 1, Table 4).

We compared our prognostic model with classic IPI and NCCN-IPI using the C-index (Fig. 2, Table 5). The C-indices for classic IPI, NCCN-IPI, and current prognostic model were 0.705 (95% CI, 0.659–0.751), 0.710 (95% CI, 0.664–0.757), and 0.739 (95% CI, 0.691–0.786), respectively. The calibration slope for classic IPI, NCCN-IPI, and current prognostic model are demonstrated in Table 5.

Following model fitness test for discrimination and analysis for model performance for predicting probabilities, we conducted an external validation of PROCESS dataset. The five-year OS rates were 96.3%, 87.4%, 73.2%, and 37.0% for the low-, low-intermediate-, high-intermediate-, and high-risk group, respectively (Fig. 1, Table 4). These results indicate that our model has high prognostic capability in PROCESS cohort.

DISCUSSION

In this study, we proposed a new prognostic model for DLBCL that can be easily applied in the clinical setting and has favorable discriminative capability. Although molecular analysis of DLBCL was enabled to distinguish the molecular feature and prognosis based on tumor biology, a more accurate clinical prognostic index that can be used in daily practice is needed in the rituximab era. Recently proposed NCCN-IPI showed significantly enhanced predictive performance [11]. Thereafter, the validity of NCCN-IPI has been tested in various ethnicities and specific disease status (e.g., localized DLBCL) [18, 19]. This improvement of risk stratification of NCCN-IPI results from 2 modifications of original IPI: subdivision of existing continuous variables of age and LDH into 4 and 3 subgroups, respectively, and revision of the number of extranodal involvement into specific sites of involvement. With the refined categorization of age and LDH, the superior discriminative function of NCCN-IPI is expected to increase its predictive capability. A computer program-based prognostic model that uses continuous variables without categorization might have a more accurate discriminative capability. However, physician's adherence to clinical prognostic models needs to be considered. The refined categorization of age and LDH can be a limitation for the clinical application of prognostic model. As such, the prospective model suggested in this study can be easily applicable and useful model in the rituximab era.

Notably, the presence of GI involvement in patients with DLBCL represented favorable RFS and OS in current study. This result agrees with that of previous studies which suggested that primary GI involvement in patients with DLBCL was associated with favorable survival outcomes [20, 21]. However, among the modifications from original IPI in NCCN-IPI is the presence of extranodal sites because the BM, CNS, liver/GI tract, or lung involvement was shown to confer a more negative prognostic feature than the number of extranodal sites. Interestingly, the prognostic implication of GI tract involvement in patients with DLBCL may have a geographic difference. The favorable outcomes in patients with DLBCL with GI tract involvement, reported in a study conducted in Japan, indicate that the different prognostic implications of GI involvement may be a result of geographic difference. Consequently, this opposite effect on survival outcome of GI involvement may limit the discriminative function of NCCN-IPI in our cohort. Given the lack of reliable data for the prognostic effect according to extranodal involvement sites in different ethnicities, large-scale studies

to assess the validity of NCCN-IPI needs to be conducted in Eastern countries.

β2MG is a powerful prognostic factor in aggressive and indolent non-Hodgkin lymphoma and Hodgkin lymphoma [13-15]. The prognostic value of serum β2MG, which was identified in the early 1970s, has been investigated in multiple myeloma and lymphoma. While the mechanism of β2MG as a prognostic factor remains unclear, serum soluble β2MG is currently accepted as marker of tumor burden [12] because β2MG is released from the cell surface or cytoplasm and is associated with cell proliferation. Previous reports that demonstrated the prognostic implication of β2MG in lymphomas also showed that serum β2MG is significantly correlated with treatment efficacy and survival outcomes. In a cooperative study that proposed the Follicular Lymphoma International Prognostic Index, the serum β2MG was significantly associated with OS [22]. In non-gastric marginal zone lymphoma, serum β2MG also showed significant association with RFS and OS [13]. Furthermore, the prognostic implication of serum β2MG in patients with DLBCL was documented in a large-scale, single-center retrospective study [23]. In this study, the prognostic relevance of β2MG was retained in multivariate analysis along with IPI. A recent retrospective study assessed the validity of NCCN-IPI in 499 European patients with DLBCL and analyzed the effect of using additional laboratory parameters in conjunction with NCCN-IPI in predicting disease prognosis [17]. The study confirmed the validity of the NCCN-IPI in a European cohort and revealed that serum β2MG and albumin are independent prognostic factors for survival in multivariate analysis. Moreover, it suggested that serum albumin and β2MG are likely to provide significant prognostic information to the NCCN-IPI. These findings indicate the advantage of serum β2MG as a convenient prognostic marker in patients with DLBCL.

Our study has several limitations; thus, the results should be interpreted carefully. Our study was retrospectively conducted in single center based on prospectively collected data. However, we confirmed the validity of our prognostic model in a multicenter prospective cohort (PROCESS).

In conclusion, we demonstrated the predictive capability and relevance of the new prognostic model for DLBCL in the rituximab era. Our model includes age, LDH, ECOG PS, Ann Arbor stage, and β2MG as prognostic factors, has promising discriminative power, and is convenient to apply. However, further validations using an independent cohort are warranted.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Supplementary Table 1. Five-year overall survival and 5-year relapse-free survival according to the number and site of extranodal involvement in AMC cohort.

	5-yr OS			5-yr RFS		
	5-yr OS	SE	*P*	5-yr RFS	SE	*P*
N of extranodal site						
<2	81.80%	2.10%	<0.001	85.60%	1.90%	<0.001
≥2	64.40%	3.80%		68.30%	3.30%	
Extranodal involvement in bone marrow, CNS, liver/GI tract, or lung						
No	76.50%	2.70%	0.548	82.20%	2.30%	0.088
Yes	75.70%	2.70%		77.20%	2.50%	
Involvement of extranodal site						
Bone marrow						
No	78.00%	2.00%	0.007	82.10%	1.80%	<0.001
Yes	63.70%	6.10%		66.00%	5.00%	
Liver						
No	77.10%	2.00%	<0.001	82.60%	1.60%	<0.001
Yes	55.40%	9.20%		51.60%	8.90%	
GI tract						
No	72.50%	2.50%	0.013	77.70%	2.10%	0.099
Yes	83.60%	2.80%		83.60%	2.80%	
Lung						
No	77.80%	2.00%	<0.001	81.80%	1.80%	<0.001
Yes	56.90%	7.00%		55.80%	6.90%	
Genitourinary tract						
No	77.10%	1.90%	<0.001	80.60%	1.70%	<0.001
Yes	23.50%	17.70%		42.40%	13.50%	
Bone						
No	75.80%	1.90%	<0.001	81.60%	1.70%	<0.001
Yes	56.00%	8.30%		63.00%	6.10%	

Abbreviations: CNS, central nervous system; GI, gastrointestinal; OS, overall survival; RFS, relapse-free survival; SE, standard error.