

Comparison of Prognostic Indices in Japanese Patients with Diffuse Large B-cell Lymphoma in the Yonago Area

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ABSTRACT

Background Several prognostic indices for diffuse large B-cell lymphoma (DLBCL) have been developed. Which index is appropriate for Japanese patients with DLBCL treated in real-world practice is unknown.

Methods The prognostic performances of the original international prognostic index (IPI), age-adjusted IPI, National Comprehensive Cancer Network-IPI, elderly IPI and revised IPI were compared using patients with DLBCL treated in a single institute in the Yonago area in Japan.

Results From 2005 through 2015, 182 patients with de novo DLBCL were treated with chemotherapy in Tottori University Hospital; 154 (85%) patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) although full dose was administered in 63 (35%) patients. The median age of the patients was 71 years (range 18 to 91). Three-year overall survival rate was 71.8% (95% CI, 64.1% to 78.2%). All indices significantly discriminate risk groups for overall survival of the patients ($P < 0.001$). Although no statistical difference of performance was found among these indices, the best scores of model fit/discrimination measures were beaten out by age-adjusted IPI, the simplest and three-factor model.

Conclusion Age-adjusted IPI is still usable in real-world practice while a better predictive model is desired for Japanese patients with DLBCL.

Key words lymphoma, large B-cell, diffuse; prognosis; rituximab; aged; Japan

The International Prognostic Index (IPI) is a prognostic model developed in 1993, using 3273 patients of all ages with aggressive non-Hodgkin lymphoma treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like chemotherapy.¹ The five pretreatment risk factors, i.e., age (≤ 60 vs. > 60), tumor stage (stage I or II vs. stage III or IV), number of extranodal sites of disease (≤ 1 vs. > 1), performance status (0 or 1 vs. ≥ 2) and serum lactate dehydrogenase level (≤ 1 vs. > 1 times normal), were identified and four risk categories

were made. Patients with the number of risk factors 4 or 5 were assigned to a high-risk group, 5-year survival of which was 26%. In addition, using 1274 patients aged 60 years or younger, age-adjusted IPI was also made based on tumor stage, lactate dehydrogenase and performance status because the age limit for patients treated by most intensive experimental regimens for non-Hodgkin's lymphoma was 60 years.¹ In the advent of rituximab, the prognosis of B-cell lymphoma improved dramatically and the IPI is no longer potent especially in discriminating the subgroup of patients with poor prognosis. Then, new prognostic models were developed and evaluated for predicting the prognosis of patients with diffuse large B-cell lymphoma (DLBCL), a major subtype of aggressive lymphoma; these are revised IPI,² elderly IPI³ and National Comprehensive Cancer Network (NCCN)-IPI.⁴ The revised-IPI regrouped the original IPI factors into 3 risk categories.² The elderly IPI used the cut-off point of age at 70 years instead of 60 years in the IPI.³ The NCCN-IPI subdivided age to 4 levels (≤ 40 vs. > 40 to ≤ 60 vs. > 60 to ≤ 75 vs. > 75) and lactate dehydrogenase into 3 levels (≤ 1 vs. > 1 to ≤ 3 vs. > 3 times normal).⁴ In addition, the involvement of bone marrow, liver/gastrointestinal tract, lung and/or central nervous system was considered as a factor instead of the number of extranodal sites of disease. These indices were elaborated based on clinical data of non-Japanese patients and which index is appropriate for Japanese patients with DLBCL treated in real-world practice is unknown.

Tottori University Hospital is a tertiary hospital located in Yonago City with a population of 148,000 inhabitants, surrounded by a rural area in Tottori prefecture, where the population is rapidly ageing and the proportion of people aged older than 65 years was

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Abbreviations: AIC, Akaike's information criteria; AUC, area under the receiver operator characteristics curve; CI, confidence interval; CPE, concordance probability estimate; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival

27.6% according to the national census in 2015. In this area, our hospital is one of the two hospitals in which patients with lymphoma are treated with curative intent. We reviewed the clinical records of Japanese patients with DLBCL treated in Tottori University Hospital from 2005 through 2015 and compared the predictive power of these indices.

MATERIALS AND METHODS

Patients and Methods

This study is a retrospective analysis of an unselected patients with newly diagnosed de novo DLBCL who were consecutively treated in Tottori University Hospital from April 2005 through December 2015. Patients were included for analysis in this study if they received any anti-cancer drug and were at least 16 years old at the time of treatment and the clinical records were reviewed. R-CHOP immunochemotherapy was the standard regimen and 80% dose of doxorubicin, vincristine and cyclophosphamide was delivered in patients older than 80 years of age and subsequent dose was adjusted at the doctor's discretion. For frail patients, doxorubicin and/or other drugs were removed from the regimen and even ad libitum administration of a couple of drugs was done. In case of central nervous system involvement, R-MPV (rituximab, methotrexate, procarbazine and vincristine) regimen was preferred.⁵ The study was approved by the Ethics Committee at Tottori University Faculty of Medicine (approval number 2489).

Statistical methods

Overall survival (OS) was calculated from the date of initial chemotherapy until death from any cause. Progression-free survival (PFS) was calculated from the date of initial chemotherapy to documented disease progression, relapse and death from any cause; observations were censored on the date the patient was last known to be alive. The follow-up cut-off point was December 31, 2016. OS and PFS were assessed using the Kaplan-Meier method and risk groups were compared using the log-rank test. Performances of prognostic indices were compared by a measure of global fit (Akaike's information criteria, AIC) and by a measure of discrimination (concordance probability estimate, CPE).^{6,7} Low values of AIC indicate better fit and high values of CPE indicate better discrimination. The area under the receiver operator characteristic curve (AUC) over time was also used to compare between these indices and an integrated AUC was calculated as a time-dependent concordance measure.⁸ Univariate and multivariate analysis of prognostic factors was performed using the Cox proportional hazard regression model. Data were analyzed using EZR (ver. 1.36)⁹ and R (ver. 3.4.0) software.

RESULTS

Patients and treatments

From April 2005 through December 2015, 196 patients with newly diagnosed de novo DLBCL were identified in the clinical records in Tottori University Hospital. Four patients with DLBCL were not treated with chemotherapy and thus excluded from the study; 2 were observed after methotrexate discontinuation, 1 received whole brain irradiation for palliative care and 1 underwent splenectomy only. Ten patients with missing values were also excluded. Baseline clinical characteristics of 182 patients were shown in Table 1. The median age of the patients was 71 years (range 18 to 91); 41 patients were 80 years old or more. Reduced performance status (> 1) was found in 43% and advanced disease (III and IV) was in 54%. Most patients (152 of 182, 85%) received R-CHOP immunochemotherapy.¹⁰ However, only 63 patients received full dose, 58 of whom completed 6 cycles. Dose was reduced in 91 (50%) of 182 patients (Table 2), 74 of whom completed treatment. For patients with diabetes mellitus, the dose of prednisolone was frequently reduced. The remaining 28 patients receive other chemotherapies. Three patients underwent front-line stem-cell transplantation (2 autologous and 1 allogeneic transplants). Five patients received consolidative radiation therapy to a site of bulky or residual disease. A variety of salvage regimens were used for refractory/relapsed patients. The most frequent regimen used as a second-line treatment for fit patients was R-ICE (rituximab, ifosfamide, carboplatin and etoposide) regimen followed by high-dose chemotherapy and autologous stem-cell transplantation.¹¹

Outcome of all patients

The median follow-up time for living patients is 3.7 years. The median survival time of all patients was not reached, and 3-year OS was 72% (95% CI, 64% to 78%) (Fig. 1A). The median PFS was 5.8 years (95% CI, 4.5 years to NA), and 3-year PFS was 66% (95% CI, 58% to 73%) (Fig. 2A).

Overall survival according to prognostic indices

Outcomes of OS according to the indices are listed in Table 3 and are shown in Figs. 1B to F. Patients were evenly distributed between risk categories in the original IPI, age-adjusted IPI and elderly IPI while the patient number was skewed to the high-intermediate-risk category in NCCN-IPI and to the poor-risk category in revised IPI. The indices with 4 categories were predictive in this cohort and significantly discriminate risk groups ($P < 0.001$, log-rank test) with 3-year OS of low-risk, low-intermediate-risk, high-intermediate-risk, high-risk

Table 1. Baseline clinical characteristics of patients

Characteristics	N	%
Age*, y		
≤ 40	9	5
> 40 to ≤ 60	34	19
> 60 to ≤ 75	75	41
> 75	64	35
Male gender	106	58
ECOG PS > 1	78	43
Ann Arbor stage (III or IV)	99	54
LDH, normalized		
≤ 1	67	37
> 1 to ≤ 3	90	49
> 3	25	14
More than 1 extranodal site involvement	127	70
Bone marrow involvement	8	4
Liver/Gastrointestinal tract involvement	58	32
Lung involvement	3	2
CNS involvement	10	5

*Median, 71 years; range, 18 to 91. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; y, years.

Table 2. Treatment

Treatment	N	%
R-containing regimen	175	96
R-CHOP, full dose	63	35
R-CHOP, reduced dose	91	50
R-COP	5	3
R only	4	2
R-MPV	3	2
DA-EPOCH-R	2	1
Other regimens*	7	4
Non-R regimen	7	4
CHOP	2	1
Other regimens*	5	3

*Various treatments including ad libitum administration of a couple of drugs. CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; COP, cyclophosphamide, vincristine and prednisolone; DA-EPOCH, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin; MPV, methotrexate, procarbazine and vincristine; R, rituximab.

groups ranging from 92% to 100%, 77% to 84%, 67% to 72% and 46% to 51%, respectively although separation between low-intermediate-risk and high-intermediate-risk groups was poor. Revised IPI also significantly discriminates risk groups ($P < 0.001$, log-rank test).

Progression-free survival according to prognostic indices

Outcomes of PFS according to the indices are listed

in Table 3 and are shown in Figs. 2B to F. All indices significantly discriminate risk categories ($P < 0.001$, log-rank test except revised IPI for which $P = 0.002$) although poor separations between risk groups were frequently found.

Comparison of prognostic indices

To compare the predictive power of prognostic indices, we used AIC, CPE and AUC. AIC, CPE and integrated AUC are listed in Table 4 and AUCs of these indices are shown in Fig. 3. No statistical difference of performance was found among these indices. However, the best scores of model fit/discrimination measures were beaten out by age-adjusted IPI. In addition, AUC of age-adjusted IPI is better than those of other indices over time.

Significance of prognostic factors

To see the significance of prognostic factors used in these indices, univariate and multivariate analysis for OS and PFS was performed with the current cohort. P values are shown in Table 5 and age is not a significant factor regardless of cut-off point. Only number of extranodal sites and performance status remains significant in multivariate analysis.

DISCUSSION

The outcome of all the patients is comparable to that of the first study reporting the superiority of R-CHOP over CHOP chemotherapy in patients aged 60 to 80 years; 2-year OS was 70% (95% CI, 63 to 77) for the R-CHOP group in the report¹⁰ vs. 78% (95% CI, 69 to 85) for the patients of the same age group in the current cohort. Even for 64 patients older than 75 years, 2-year OS was 73% (95% CI, 59 to 82). Rituximab was administered in 96% of patients in this cohort while a variety of regimens were used, suggesting a survival benefit of rituximab.

The NCCN-IPI was developed to improve risk stratification by putting weights on age and lactate dehydrogenase and by restricting extranodal diseases, and successfully identified a high-risk group with 5-year OS of 33%. Nakaya et al. evaluated NCCN-IPI using 284 Japanese patients and found no statistically significant discriminant power in their cohort.¹² On the contrary, Yamada et al. reported a significant discriminant power of NCCN-IPI using a Japanese cohort of a similar sample size.¹³ In this study, NCCN-IPI was a predictable model. And, the outcome of a high-risk group was more favorable than that of the original report although a substantial number of patients were treated with reduced doses of R-CHOP regimen. It may be reflected by the fact that extranodal disease and age were not significant

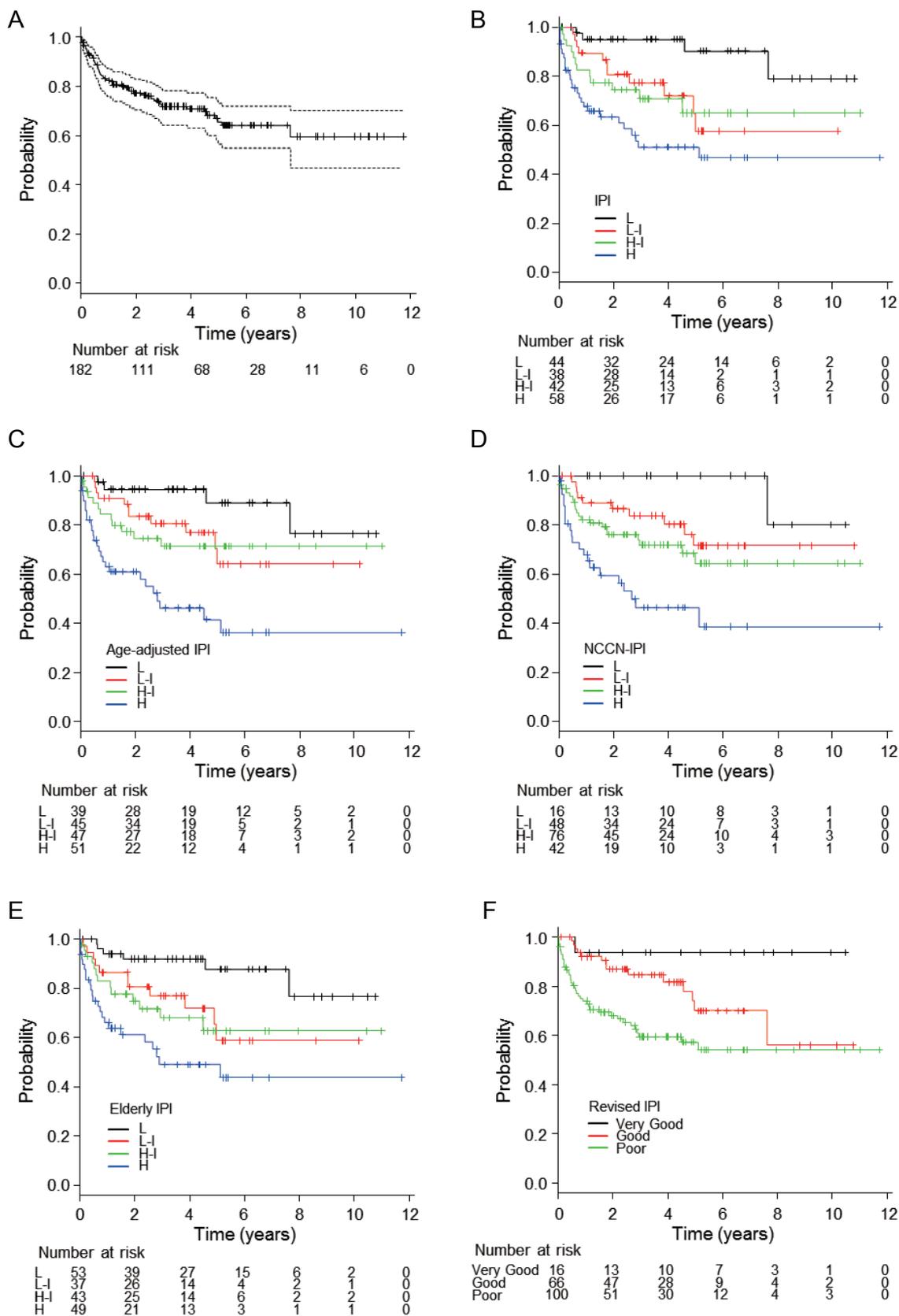


Fig. 1. Overall survival (OS). (A) OS of all patients (solid line) with 95% confidence interval (dotted line). (B–F) OS according to the original international prognostic index (IPI) (B), age-adjusted IPI (C), National Comprehensive Cancer Network (NCCN)-IPI (D), elderly IPI (E) and revised IPI (F). L, low-risk (black); L-I, low-intermediate risk (red); H-I, high-intermediate risk (green); H, high risk (blue); very good, very good risk (black); good, good risk (red); poor, poor risk (green).

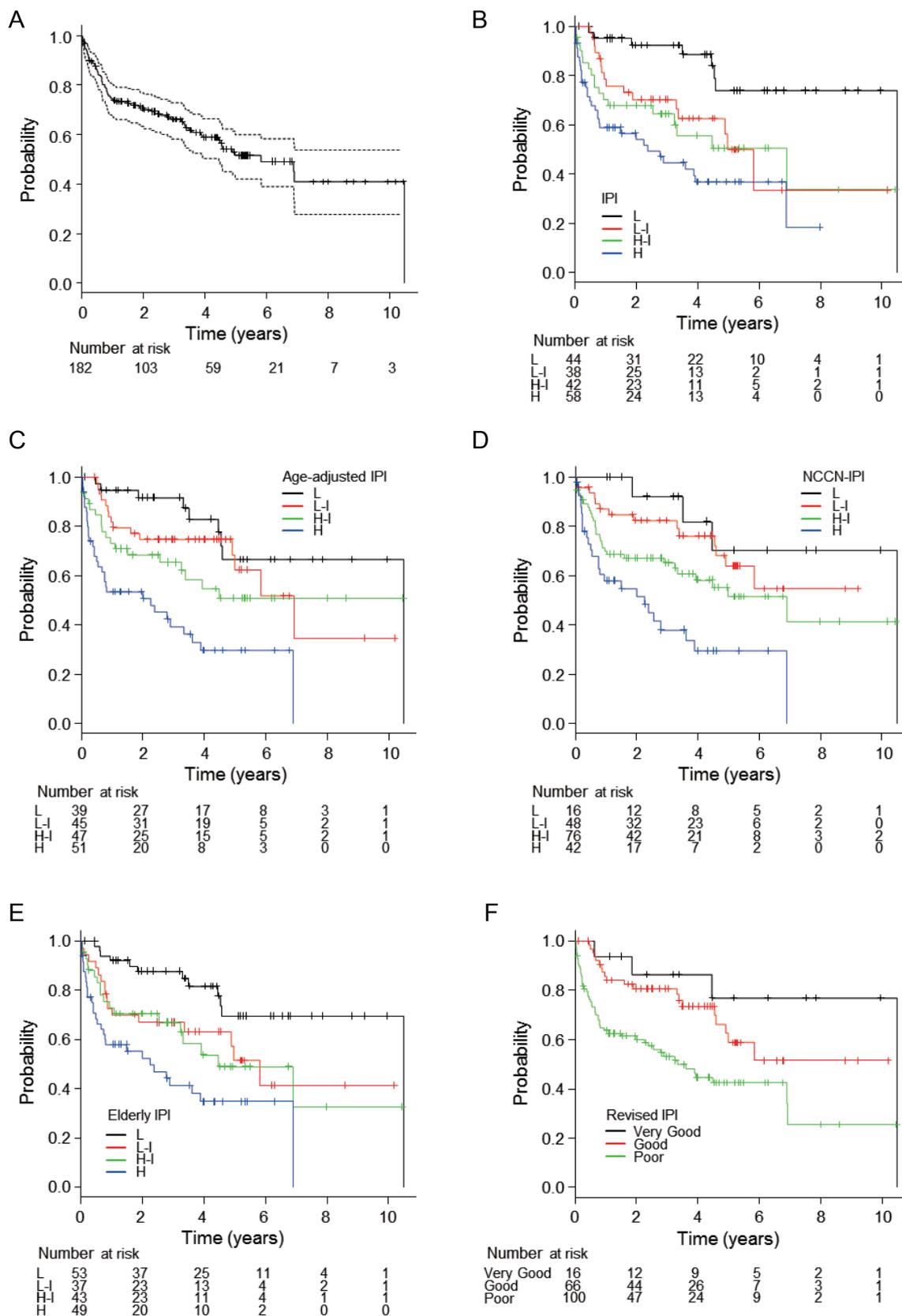


Fig. 2. Progression-free survival (PFS). (A) PFS of all patients (solid line) with 95% confidence interval (dotted line). (B–F) PFS according to the original international prognostic index (IPI) (B), age-adjusted IPI (C), National Comprehensive Cancer Network (NCCN)-IPI (D), elderly IPI (E) and revised IPI (F). L, low-risk (black); L-I, low-intermediate risk (red); H-I, high-intermediate risk (green); H, high risk (blue); very good, very good risk (black); good, good risk (red); poor, poor risk (green).

Table 3. Distribution and outcomes of patients according to prognostic indices

Index, Risk category	Factors	Patients N (%)	OS			PFS		
			Estimated 3-year (95% CI)	Estimated HR (95% CI)	Wald <i>P</i> value	Estimated 3-year (95% CI)	Estimated HR (95% CI)	Wald <i>P</i> value
IPI								
Low	0, 1	44 (24)	95 (82, 99)	0.52 (0.36, 0.74)	< 0.001	95 (81, 99)	0.57 (0.43, 0.75)	< 0.001
Low intermediate	2	38 (21)	77 (60, 88)	0.70 (0.49, 1.00)	0.048	79 (61, 90)	0.74 (0.54, 0.99)	0.044
High intermediate	3	42 (23)	70 (52, 83)	0.54 (0.27, 1.08)	0.080	73 (55, 84)	0.63 (0.35, 1.13)	0.120
High	4, 5	58 (32)	51 (36, 64)	1		58 (42, 71)	1	
Age-adjusted IPI								
Low	0	39 (21)	95 (80, 99)	0.50 (0.35, 0.71)	< 0.001	94 (79, 99)	0.58 (0.44, 0.75)	< 0.001
Low intermediate	1	45 (25)	80 (64, 90)	0.58 (0.41, 0.83)	0.003	85 (69, 93)	0.56 (0.41, 0.77)	< 0.001
High intermediate	2	47 (26)	71 (54, 83)	0.40 (0.20, 0.80)	0.009	73 (57, 84)	0.50 (0.28, 0.88)	0.017
High	3	51 (28)	46 (31, 61)	1		51 (34, 66)	1	
NCCN-IPI								
Low	0, 1	16 (9)	100	0.40 (0.20, 0.79)	0.009	92 (57, 99)	0.54 (0.36, 0.81)	0.003
Low intermediate	2, 3	48 (26)	84 (69, 92)	0.54 (0.37, 0.79)	0.001	86 (72, 94)	0.54 (0.39, 0.76)	< 0.001
High intermediate	4, 5	76 (42)	72 (59, 81)	0.45 (0.25, 0.83)	0.010	78 (66, 86)	0.50 (0.29, 0.85)	0.010
High	6–8	42 (23)	46 (29, 62)	1		48 (29, 65)	1	
Elderly IPI								
Low	0, 1	53 (29)	92 (80, 97)	0.54 (0.40, 0.74)	< 0.001	94 (81, 98)	0.60 (0.48, 0.76)	< 0.001
Low intermediate	2	37 (20)	77 (59, 88)	0.70 (0.48, 0.99)	0.044	73 (55, 85)	0.72 (0.53, 0.98)	0.037
High intermediate	3	43 (24)	67 (49, 80)	0.55 (0.28, 1.09)	0.086	75 (57, 86)	0.55 (0.30, 1.00)	0.051
High	4, 5	49 (27)	49 (33, 63)	1		55 (37, 70)	1	
Revised IPI								
Very good	0	16 (9)	94 (63, 99)	0.35 (0.13, 0.94)	0.037	92 (57, 99)	0.48 (0.27, 0.87)	0.015
Good	1, 2	66 (36)	85 (73, 92)	0.45 (0.24, 0.83)	0.010	86 (75, 93)	0.45 (0.27, 0.76)	0.003
Poor	3–5	100 (55)	59 (48, 69)	1		64 (53, 74)	1	

Hazard ratios in Cox models with the high-risk or poor-risk category as the reference group are shown. All indices significantly discriminate risk groups ($P < 0.001$, log-rank test except PFS by revised IPI for which $P = 0.002$).

CI, confidence interval; HR, hazard ratio; IPI, international prognostic index; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival.

predictive factors in the current cohort probably because of a small sample size and a short follow-up period (Table 5). However, NCCN-IPI was considered less predictable in older population.^{13–15} Even elderly IPI, which was made for older population, had no improvement found in this cohort.

Age-adjusted IPI, in which age is excluded from explanatory factors, was initially developed as a simplified model of the original IPI for patients aged 60 years or younger. Based on AIC, CPE and AUC, age-adjusted IPI was found to be the best model in this cohort, the median age of which was older than 70 years. Again, it may be reflected by the fact that age was not significant predictive factor. The starting dose of cyclophosphamide, doxorubicin and vincristine in R-CHOP for patients older than 80 years of age was 80% of the protocol in our hospital and subsequent dose was adjusted if necessary. The dose is relatively higher than that proposed for elderly patients,^{16, 17} which might improve the outcome of

the elderly.

Modification of NCCN-IPI was attempted to improve the model's discrimination although validation was not performed yet.^{13, 15, 18} A better IPI is desired for ageing Japanese patients with DLBCL to discriminate the subgroup of patients with poor prognosis. The median follow-up period of 3.7 years was not enough to estimate a 5-year OS in the current cohort and 5-year OS rates of a high-risk groups defined by NCCN-IPI and by age-adjusted IPI was 46% (95% CI, 29% to 62%) and 42% (95% CI, 25% to 57%), respectively. Although longer follow-up is necessary, age-adjusted IPI is still usable for real-world practice in the Yonago area.

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The authors declare no conflict of interest.

Table 4. Performance of prognostic indices

Index	AIC		CPE (SE)		iAUC	
	OS	PFS	OS	PFS	OS	PFS
IPI	493	675	0.658 (0.032)	0.645 (0.028)	0.663	0.653
Age-adjusted IPI	489	671	0.673 (0.031)	0.657 (0.027)	0.677	0.661
NCCN-IPI	493	676	0.654 (0.031)	0.638 (0.028)	0.660	0.644
Elderly IPI	493	676	0.658 (0.031)	0.640 (0.027)	0.663	0.648
Revised IPI	497	680	0.633 (0.032)	0.618 (0.028)	0.632	0.626

Low values of AIC indicate better fit and high values of CPE and iAUC indicate better discrimination and concordance, respectively. AIC, Akaike's information criteria; CPE, concordance probability estimate; iAUC, integrated area under the receiver operator curve over time; IPI, international prognostic index; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival.

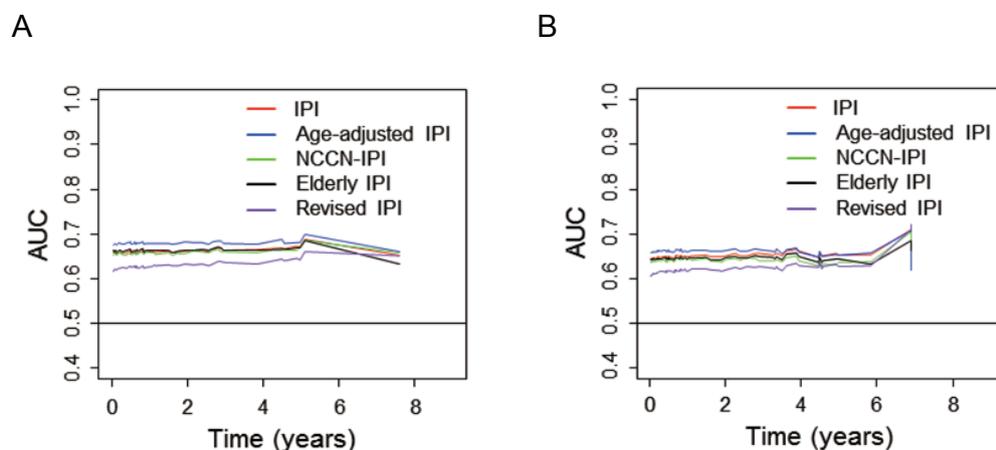


Fig. 3. Time weighted area under the receiver operator characteristics curves (AUC). (A, B) AUC for overall survival (A) and progression-free survival (B) according to the original international prognostic index (IPI) (red), age-adjusted IPI (blue), National Comprehensive Cancer Network (NCCN)-IPI (green), elderly IPI (black) and revised IPI (purple).

Table 5. Univariate and multivariate analysis for prognostic factors

Factor	OS		PFS	
	Univariate	Multivariate	Univariate	Multivariate
Age (years)				
≤ vs. > 60	0.172		0.168	
< vs. ≥ 70	0.312		0.659	
< 40 vs. 41–60 vs. 61–75 vs. > 75	0.098		0.109	
LDH, normalized				
≤ vs. > 1	0.008		0.005	
≤ 1 vs. > 1 to ≤ 3 vs. > 3	< 0.001		0.002	
ECOG PS ≤ vs. > 1	< 0.001	< 0.001	< 0.001	< 0.001
Ann Arbor stage I or II vs. III or IV	0.003		< 0.001	
Number of extranodal sites ≤ vs. > 1	0.001	0.010	< 0.001	0.003
Extranodal disease* vs. none	0.447		0.513	

P values are shown. *Lymphomatous involvement of the bone marrow, liver/gastrointestinal tract, lung and/or central nervous system. ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

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