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Enhanced international prognostic index in Japanese patients with diffuse large B-cell lymphoma

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ABSTRACT

To evaluate the National Comprehensive Cancer Network (NCCN) International Prognostic Index (IPI), we analyzed 284 patients treated with the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in our institution in Japan. Their 5-year overall survival (OS) by risk level was 80.7%, 74.8%, 55.4% and 67.5% ($P=0.005$); and their 5-year progression-free survival (PFS) was 76.8%, 78.6%, 63.7% and 58.3% ($P=0.0722$). The NCCN-IPI is a simple scale that uses conventional clinical factors, but did not reflect survival in our cohort. The NCCN-IPI may require further evaluation for different regions and ethnicities before adopting it for routine clinical use.

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1. Introduction

Recently Zhou et al. developed the new National Comprehensive Cancer Network (NCCN)- International Prognostic Index (IPI) to predict survival in the rituximab era more accurately than the older IPI system [1]. Although reports that used the same prognostic stratification have since been published from various geographic regions, whether these results can be extrapolated to different ethnic populations is unclear. We therefore aimed to validate the NCCN-IPI in the presumably less selected population of Japanese patients with diffuse large B cell lymphoma (DLBCL).

2. Materials and methods

We included 284 patients who were consecutively diagnosed with DLBCL and treated with first-line rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (r-CHOP), or R-CHOP-like treatment at Kansai Medical University Hospital during 2006–2014 in this retrospective analysis. This study was approved by the Ethics Committee of Kansai Medical University. Patient survival was analyzed with the Kaplan–Meier method, and

results were compared by log-rank and Cox proportional hazards models. $P < 0.05$ was considered significant. All statistical analyses were performed using EZR (modified R software, Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

Mean age of these patients was 67 years old (range: 20–91 years). The NCCN-IPI classified 11% of patients being as low risk, 36% as low-intermediate (LI), 47% as high-intermediate (HI) and 6% as high risk (Table 1). Compared to the older IPI, fewer patients were classified as low- or high-risk and more as LI and HI. The NCCN-IPI failed to identify four prognostic groups of patients in our cohort. Our patients' 5-year overall survival (OS) rates were low-risk: 80.7%; LI: 74.8%; HI: 55.4%; and high-risk: 67.5% ($P=0.005$) (Fig. 1.(A)). Their 5-year progression-free survival (PFS) rates were low-risk: 76.8%; LI: 78.6%; HI: 63.7%; and high-risk: 58.3% ($P=0.0722$) (Fig. 2.(A)). For patients who did not receive upfront autologous hematopoietic stem cell transplantation (ASCT), the 5-year OS rates were low-risk: 80.7%; LI: 76.5%; HI: 53.2%, and high-risk: 63.5% ($P=0.00137$) (Fig. 1.(B)). Their 5-year PFS rates were low-risk: 76.8%; LI: 80.3%; HI: 58.7%; and high-risk: 63.6% ($P=0.123$) (Fig. 2.(B)).

In multivariate analysis, low albumin level (< 3.5 g/dl) was an independent predictor of shorter OS, although lactate dehydrogenase (LDH), hemoglobin (Hb), C-reactive protein (CRP),

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Table 1
Patients' characteristics.

No. of patients (n)	284
Median age, range(y/o)	67(20–91)
40 \geq (%)	5
> 40 to \leq 60(%)	23
> 60 to \leq 75(%)	49
> 75 (%)	23
Male sex (%)	61
IPI/aalIPI (%)	
Low	37
Low-intermediate	16
High-intermediate	19
High	28
NCCN-IPI (%)	
Low	11
Low-intermediate	36
High-intermediate	47
High	6
Stage(%)	
I	23
II	14
III	19
IV	44
Elevated LDH level (%)	48
Extranodal disease > 1 (%)	40
upfront ASCT(%)	9

LDH: lactate dehydrogenase
ASCT: autologous hematopoietic stem cell transplantation

age, sex, stage, extranodal involvement, and ASCT were not (Table 2).

4. Discussion

Although the NCCN-IPI was developed to improve stratification of high-risk patients with DLBCL (i.e., whose 5-year OS < 50%), it failed to detect them in our analysis; the HI group had shorter 5-year OS than the high-risk group (Fig. 1 A.).

In our institute, most eligible high-risk or HI patients were treated with upfront ASCT, which we assumed would improve their survival. When we excluded these patients from our analysis, the poorer 5-year OS for the HI group compared with the high-risk group was even more pronounced (Fig. 1 B.).

As the NCCN-IPI attaches more weight on age in the 4 risk groups, we supposed that its failure to predict outcome in this study was because our patients were older than original cohort; thus prognoses of patients whose high scores were due to age rather than tumor burden (as indicated by LDH or stage) might not be accurately predicted in the NCCN-IPI system. Some reports described results similar to ours, showing that NCCN-IPI failed to accurately predict outcomes for elderly patients [4,7].

Aside from LDH, information about how other important parameters affect NCCN-IPI results have not been published, as far as we know. Hemoglobin [2], albumin [3,4], and CRP [5] have been found to be independent prognostic factors in aggressive lymphoma. As these reported parameters were routinely available in our patients' records, we analyzed their effects on OS, using multivariate analysis; however, we found only low albumin levels to be a significant predictor of worse 5-year OS. As albumin is usually assessed, quite easily and cheaply in standard blood laboratory tests, and is highly reproducible, it could be an important predictor, and be incorporated into a prognostic index.

Although the NCCN-IPI is a promising simple scale based on conventional clinical factors, its usefulness remains controversial

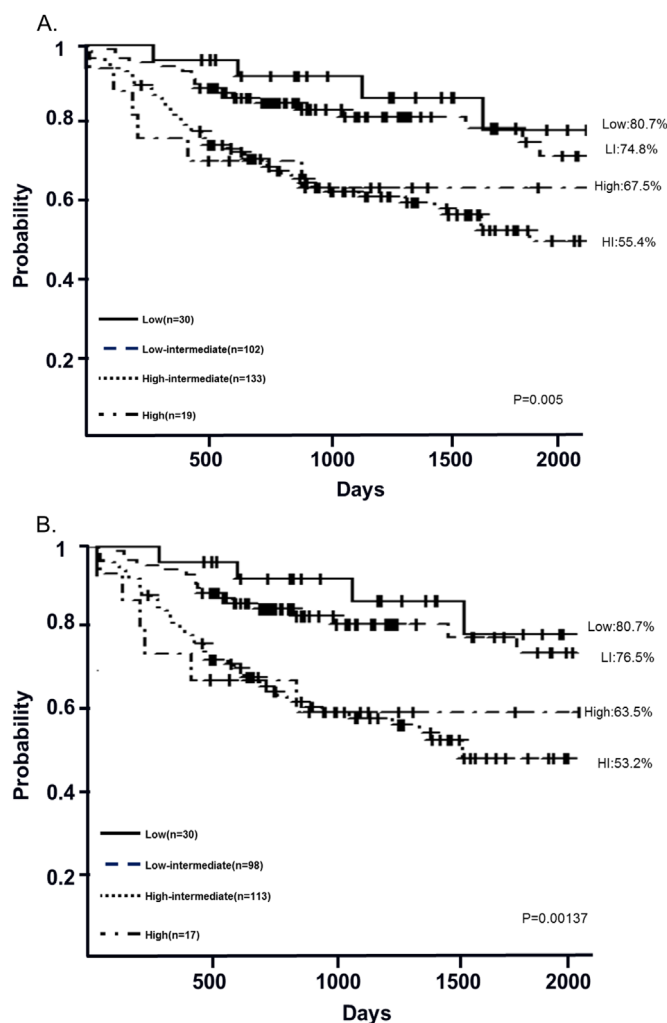


Fig. 1. Five-year OS using NCCN-IPI were 80.7%, 74.8%, 55.4%, 67.5% (p=0.005) (A). Patients without upfront ASCT(B) were 80.7%, 76.5%, 53.2%, 63.5%(p=0.00137) (B). The result revealed that patients were statistically stratified into 4-risk groups, however HI was the worst prognosis.

Table 2
Multivariate analysis.

Parameter	HR	95%CI	p value
LDH	1.106	0.681–1.793	0.684
Alb	1.949	1.121–3.386	0.018
Hb	1.088	0.666–1.775	0.737
CRP	0.986	0.333–2.912	0.980
Age	1.177	0.712–1.947	0.525
Sex	1.325	0.828–2.119	0.241
Stage	1.642	0.866–3.109	0.128
extra node	1.526	0.910–2.557	0.109
upfront ASCT	0.404	0.151–1.073	0.069

LDH: lactate dehydrogenase
Alb: albumin
Hb: hemoglobin
CRP: C-reactive protein
ASCT: autologous hematopoietic stem cell transplantation

[6,7]. It should be evaluated in populations of different regions and ethnicities before adopting it for routine clinical use.

Conflict of interest

The authors declare no competing financial interest in relation to the work.

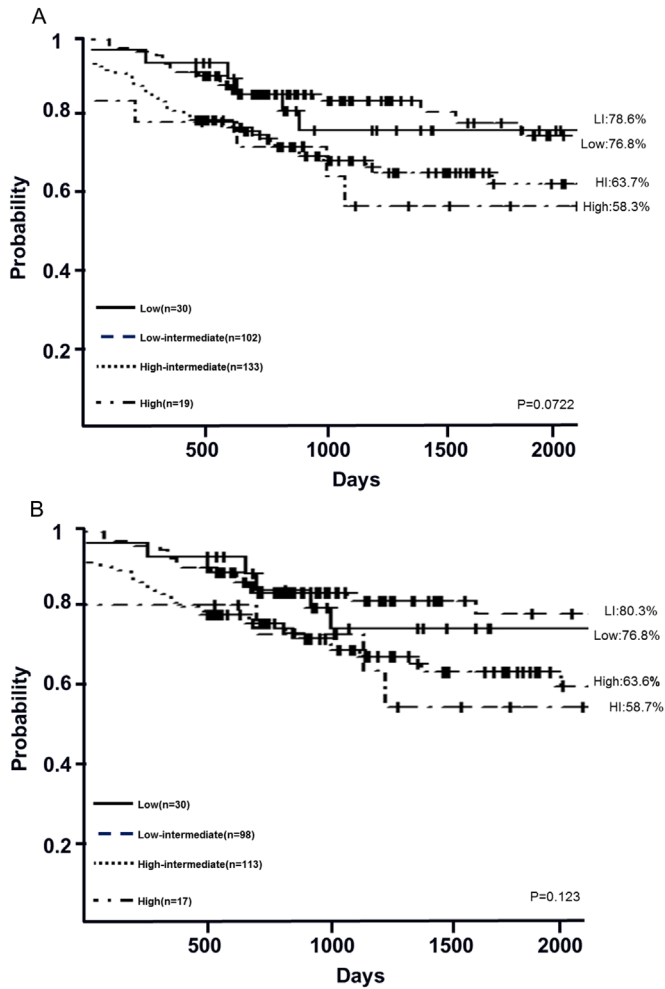


Fig. 2. Five-year PFS using NCCN-IPI were 78.6%, 76.8%, 63.7%, 58.3% ($p=0.0722$) (A). Patients without upfront ASCT(B) were 80.3%, 76.8%, 58.7%, 63.6% ($p=0.123$)(B).

References

- [1] Z. Zhou, L.H. Sehn, A.W. Rademaker, L.I. Gordon, A.S. Lacasce, A. Crosby-Thompson, et al., An enhanced International Prognostic Index (NCCN-IPI) for

- patients with diffuse large B-cell lymphoma treated in the rituximab era, *Blood* 123 (6) (2014) 837–842.
- [2] K.T. Troppan, T. Melchardt, A. Deutsch, K. Schlick, T. Stojakovic, M.D. Bullock, et al., The significance of pretreatment anemia in the era of R-IPI and NCCN-IPI prognostic risk assessment tools: a dual-center study in diffuse large B-cell lymphoma patients, *Hematol. Oncol.* 95 (6) (2015) 538–544.
- [3] O. Bairey, A. Shacham-Abulafia, O. Shpilberg, R. Gurion, Serum albumin level at diagnosis of diffuse large B-cell lymphoma: an important simple prognostic factor, *Hematol. Oncol.* (2015), <http://dx.doi.org/10.1002/hon.2233>.
- [4] T. Melchardt, K. Troppan, L. Weiss, C. Hufnagl, D. Neureiter, W. Tränkensschuh, et al., A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and β_2 -microglobulin, *Br. J. Haematol.* 168 (2) (2015) 239–245.
- [5] K. Suzuki, Y. Terui, N. Nishimura, Y. Mishima, S. Sakajiri, M. Yokoyama, et al., Prognostic value of C-reactive protein, lactate dehydrogenase and anemia in recurrent or refractory aggressive lymphoma. See comment in PubMed Commons below *Jpn. J. Clin. Oncol.* 43 (1) (2013) 37–44.
- [6] C.E. Huang, Y.Y. Chen, C.H. Lu, P.T. Chen, K.D. Lee, C.C. Chen, Validation of an enhanced International Prognostic Index (NCCN-IPI) in an Asian cohort of patients with diffuse large B cell lymphoma, *Ann. Hematol.* 94 (6) (2015) 1063–1065.
- [7] A. Yamada, H. Tamura, T. Asayama, K. Moriya, N. Okuyama, A. Kondo-Onodera, et al., Evaluation of the enhanced International Prognostic Index (NCCN-IPI) (for cases with diffuse large B-cell lymphoma, *Rinsho Ketsueki* 56 (7) (2015) 915–918. [Article in Japanese].