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Prognostic value of the Kyoto Prognostic Index in higher-risk diffuse large B-cell lymphomas treated by upfront autologous stem cell transplantation in JCOG0908 trial

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Abstract

Background: There is currently no standard prognostic model optimized for the patients with diffuse large B-cell lymphoma (DLBCL) treated with upfront intensive immunochemotherapy including autologous stem cell transplantation (ASCT). The Kyoto Prognostic Index (KPI) has been proposed as a novel prognostic model for DLBCL, which can accurately identify especially high-risk patients. In this study, we investigated the prognostic value of the KPI in JCOG0908 trial in which higher-risk DLBCL patients defined by the conventional International Prognostic Index (IPI) were treated with upfront high dose therapy followed by ASCT.

Methods: Fifty-eight patients with DLBCL, not otherwise specified, enrolled in JCOG0908 and confirmed by the central pathological review were analyzed. The Kaplan–Meier method was used to estimate the probabilities of overall survival (OS) and progression-free survival (PFS). We compared the discrimination ability of the KPI with that of the IPI.

Results: According to KPI, 3-year OS and PFS rates were 86.7% and 76.7% in low-intermediate, 73.3% and 60.0% in high-intermediate, and 61.5% and 46.2% in high-risk group. According to IPI, 3-year OS and PFS rates were 75.0% and 50.0% in low-intermediate, 82.9% and 74.3% in high-intermediate, and 63.6% and 54.5% in high-risk group. The concordance-indices of KPI and IPI were 0.642 and 0.580 for OS and 0.606 and 0.606 for PFS.

Conclusions: The KPI may be a suitable predictor of outcome than the IPI for patients with higher-risk DLBCL treated with upfront intensive immunochemotherapy including ASCT.

Key words: diffuse large B-cell lymphoma, International Prognostic Index, Kyoto Prognostic Index, autologous stem cell transplantation

Introduction

The International Prognostic Index (IPI) has been the most commonly utilized conventional prediction system for the survival outcome of diffuse large B-cell lymphoma (DLBCL) (1). However, along with the dramatic improvement of the survival outcome by the advent of rituximab-containing immunochemotherapies, the prognostic value of IPI has declined, especially among the higher-risk patients (2–4). There have been several attempts to establish prognostic indices for DLBCL in the rituximab era, such as revised IPI (R-IPI) and the National Comprehensive Cancer Network (NCCN)-IPI (4–6). Even though some of these novel prognostic indices have been widely used now for clinical care, they are unfortunately not sufficient in isolating patients at high risk of extremely poor outcome (7). Recent progress has also provided more sophisticated subcategorization of DLBCL based on patterns of genetic abnormalities and gene expression that also associated with prognosis (8–14); however, the technical complexity and high cost make it difficult to use those classifications in general. Therefore, more reliable, and clinically convenient prognostic tool is desired in daily practice.

The Kyoto Prognostic Index (KPI) has been proposed as a novel prognostic model for newly diagnosed DLBCL treated by R-CHOP or R-CHOP-like chemotherapy based on the real-world data in the Kyoto Clinical Hematology Study Group (KOTOSG) (15). KPI score can be easily assessed by serum levels of lactate dehydrogenase (LDH) and albumin (Alb), specific extranodal involvement, and patient's performance status (PS). The specific characteristic of KPI compared with the conventional IPI, R-IPI and NCCN-IPI is that it can more accurately identify extremely high-risk patients of those median overall survival (OS) period and progression-free survival (PFS) period with R-CHOP (-like) approach were shorter than 12 months, respectively. However, the prognostic value of KPI for DLBCL was constructed using a retrospective investigation of 465 patients with the median age of 70 years old, therefore, its utility should be confirmed in another prospectively registered cohort of DLBCL patients. In addition, its utility has not been evaluated in patients with DLBCL treated by upfront high-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT).

JCOG0908 trial was conducted by Japan Clinical Oncology Group (JCOG) Lymphoma Study Group to select the better induction regimen prior to upfront HDT with ASCT for newly diagnosed higher risk DLBCL patients below 65 years old (16). In this trial, all patients who responded to induction therapy received upfront HDT with ASCT and ~75% of patients survived over 5 years for the age-adjusted (aa) IPI-defined higher risk patients, however, some patients had unfavorable outcomes. As the development of a novel prognostic tool that can more accurately predict outcomes of higher risk DLBCL patients is desired, we conducted a supplementary analysis of JCOG0908 to examine if the KPI can discriminate the higher risk patients among those registered in this trial.

Materials and methods

Study design of JCOG0908

In the multicenter randomized phase II trial of JCOG0908, DLBCL patients diagnosed as high-intermediate or high risk according to the aaIPI were randomized to two arms of induction treatment either six cycles of biweekly R-CHOP or three cycles of biweekly R-CHOP followed by three cycles of CHASER (cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide and rituximab) prior to HDT designated as LEED (melphalan, cyclophosphamide, etoposide and dexamethasone) supported by ASCT. Main inclusion criteria were (i) age between 20 and 65 years old, (ii) Ann Arbor disease stage II with bulky lesion, III or IV, (iii) Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, (iv) at least one measurable lesion and (v) preserved organ functions (16). The short-term palliative use of steroids before enrollment was allowed. In that case, aaIPI, including serum LDH level, clinical stage and ECOG PS, was evaluated based on findings before steroid use. The study protocol was approved by both the JCOG Protocol Review Committee and the institutional review board of participating institutes and the trial was registered as UMIN000003823 and jRCTs031180103.

Risk stratification

The KPI was comprised of four risk factors: serum LDH level (>1–3-fold to upper limit of normal (ULN), score 1; ≥3-fold to ULN, score 2), ECOG PS (≥2, score 1), serum Alb level (<3.5 g/dl, score 1), and the presence of extranodal involvement in bone marrow, bone, skin and/or lung/pleura (score 1). Using these factors, patients are classified into four risks groups by the sum of risk score, i.e. low risk (L) (score 0), low-intermediate risk (LI) (score 1–2), high-intermediate risk (HI) (score 3) and high risk (H) (score 4–5) (15). IPI was evaluated as previously described (1).

Evaluation of KPI and IPI in the cohort of JCOG0908 by statistical analysis

Among total of 71 patients enrolled in JCOG0908 between June 2010 and February 2015, we included 60 patients with histologically confirmed DLBCL, not otherwise specified by the central pathological review. Then, two patients determined ineligible after the enrolment in JCOG0908 were excluded. Data of 58 patients were included in this analysis. Data cut-off date was 28 February 2017, and OS and PFS curves were estimated using the Kaplan–Meier method. The log-rank test was performed to compare curves according to the risk classification either by KPI or IPI. The hazard ratio was estimated using the Cox proportional hazard model. We also compared the discrimination ability of the KPI with that of the IPI by Harrell's C-index. The confidence interval (CI) was 95% for all analyses. All statistical analyses were performed by JCOG Data Center using SAS version 9.4 (SAS Institute, Cary, NC, USA). Informed consent for the secondary data use was obtained from the enrolled patients upon registration to JCOG0908.

Table 1. Patients characteristics

Characteristics	All patients (n = 58)	IPI			KPI		
		LI (n = 12)	HI (n = 35)	H (n = 11)	LI (n = 30)	HI (n = 15)	H (n = 13)
Age, median (range)	57 (28–65)	-	-	-	-	-	-
≤60 years, n (%)	44 (75.9)	12 (100.0))	29 (82.9)	3 (27.3)	24 (80.0)	10 (66.7)	10 (76.9)
≥61 years, n (%)	14 (24.1)	0 (0.0)	6 (17.1)	8 (72.7)	6 (20.0)	5 (33.3)	3 (23.1)
Serum LDH value, n (%)							
≤ULN	2 (3.4)	0 (0.0)	2 (5.7)	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)
>ULN	56 (96.6)	12 (100.0)	33 (94.3)	11 (100.0)	28 (93.3)	15 (100.0)	13 (100.0)
>1 × ULN, <3 × ULN	35 (60.3)	8 (66.7)	21 (60.0)	6 (54.5)	25 (83.3)	8 (53.3)	2 (15.4)
≥3 × ULN	21 (36.2)	4 (33.3)	12 (34.3)	5 (45.5)	3 (10.0)	7 (46.7)	11 (84.6)
ECOG PS, n (%)							
0	14 (24.1)	5 (41.7)	7 (20.0)	2 (18.2)	9 (30.0)	3 (20.0)	2 (15.4)
1	29 (50.0)	6 (50.0)	19 (54.3)	4 (36.4)	17 (56.7)	7 (46.7)	5 (38.5)
2	12 (20.7)	1 (8.3)	7 (20.0)	4 (36.4)	4 (13.3)	3 (20.0)	5 (38.5)
3	2 (3.4)	0 (0.0)	1 (2.9)	1 (9.1)	0 (0.0)	1 (6.7)	1 (7.7)
4	1 (1.7)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Ann Arbor stage, n (%)							
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
II	1 (1.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
III	15 (25.9)	6 (50.0)	8 (22.9)	1 (9.1)	10 (33.3)	4 (26.7)	1 (7.7)
IV	42 (72.4)	5 (41.7)	27 (77.1)	10 (90.9)	20 (66.7)	10 (66.7)	12 (92.3)
Serum ALB value, n (%)							
≥3.5 g/dl	31 (53.4)	5 (41.7)	22 (62.9)	4 (36.4)	25 (83.3)	6 (40.0)	0 (0.0)
<3.5 g/dl	27 (46.6)	7 (58.3)	13 (37.1)	7 (63.6)	5 (16.7)	9 (60.0)	13 (100.0)
Extranodal disease, n (%)							
0–1 site	26 (44.8)	12 (100.0)	13 (37.1)	1 (9.1)	12 (40.0)	10 (66.7)	4 (30.8)
≥2 sites	32 (55.2)	0 (0.0)	22 (62.9)	10 (90.9)	18 (60.0)	5 (33.3)	9 (69.2)
Involvement in bone marrow, bone, skin or lung/pleura	33 (56.9)	3 (25.0)	21 (60.0)	9 (81.8)	12 (40.0)	9 (60.0)	12 (92.3)

LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ALB, albmin; IPI, International Prognostic Index; KPI, Kyoto Prognostic Index; LI, low-intermediate risk; HI, high-intermediate risk; H, high risk.

Results

Patients' characteristics

Patients' characteristics are shown in Table 1. Median age of 58 analyzed patients was 57 years old (range, 28–65). With respect to risk factors included in KPI and/or IPI, 44 patients (75.9%) were below 60 years old, 56 patients (96.6%) showed increased serum LDH level including 21 patients (36.2%) with more than 3-fold increase to ULN, 43 patients (74.1%) were ECOG PS of 0–1, 57 patients (98.3%) were Ann Arbor stage III or IV, 32 patients (55.2%) had two or more extranodal sites, and 33 patients (56.9%) possessed the specific extranodal sites, bone marrow, bone, skin, and lung/pleura. Three patients whose ECOG PS improved from 3–4 to 0–2 after palliative use of steroids were enrolled in this study.

Concordance and difference in risk classification according to either by KPI or by IPI in JCOG0908

Thirty, 15 and 13 patients were classified as LI, HI and H by KPI, respectively, while 12, 35 and 11 patients were as LI, HI and H by IPI, respectively. Risk classification by KPI and IPI was concordant in 20 patients (34.5%), while was different in 38 patients. Especially, 23 (50.0%) of 46 patients with HI or H according to IPI were classified as LI by KPI, while 5 (41.7%) of 12 patients with LI according to IPI were classified as HI or H by KPI (Table 2). Thus, the risk classification by KPI and IPI was different in more than half patients.

Table 2. Distribution of patients inside risk groups by the IPI and the KPI

		KPI, n			
		Low	Low-intermediate	High-intermediate	High
IPI, n		0	30	15	13
Low	0	0	0	0	0
Low-intermediate	12	0	7	4	1
High-intermediate	35	0	20	8	7
High	11	0	3	3	5

Survival outcomes according to the IPI and the KPI

With a median follow-up of 44.6 months, 3-year OS and PFS in all 58 evaluable patients were 77.6% (95% CI, 64.6–86.3) and 65.5% (95% CI, 51.8–76.2), respectively. Both median OS and PFS are not reached during the observation period (Fig. 1). There was no difference in both OS and PFS between patients with aa-IPI defined HI and H (3-year OS; 78.3% vs. 75.0%, P = 0.97, 3-year PFS; 63.0% vs. 75.0%, P = 0.51) (Supplementary Fig. 1). According to the IPI, 3-year OS of patients with LI, HI and H were 75.0% (95% CI, 40.8–91.2), 82.9% (95% CI, 65.8–91.9) and 63.6% (95% CI,

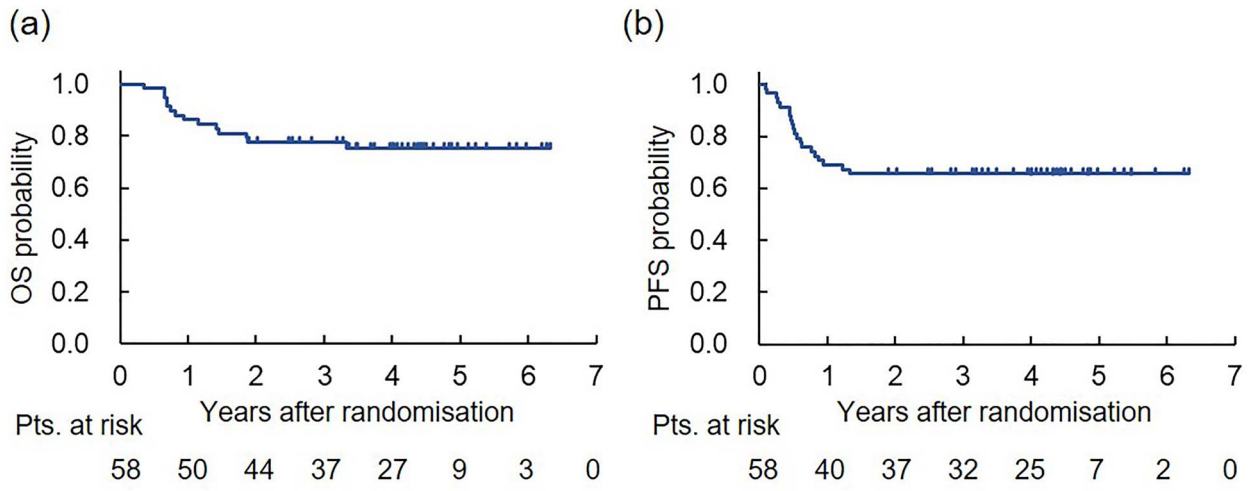

Figure 1. Overall survival (a) and progression-free survival (b) of all patients analyzed with the Kaplan–Meier method.

29.7–84.5) (P = 0.52) and 3-year PFS of those were 50.0% (95% CI, 20.8–73.6), 74.3% (95% CI, 56.4–85.7) and 54.5% (95% CI, 22.9–78.0) (P = 0.18), respectively (Fig. 2a and b). Thus, patients with IPI-defined HI showed better OS (HR 0.724, 95% CI 0.187–2.803) and PFS (HR 0.426, 95% CI 0.152–1.199) compared with patients with LI in the cohort of JCOG0908. According to KPI, 3-year OS of patients with LI, HI and H were 86.7% (95% CI, 68.3–94.8), 73.3% (95% CI, 43.6–89.1) and 61.5% (95% CI, 30.8–81.8) (P = 0.09), and 3-year PFS of those were 76.7% (95% CI, 57.2–88.1), 60.0% (95% CI, 31.8–79.7) and 46.2% (95% CI, 19.2–69.6) (P = 0.17), respectively (Fig. 2c and d). In addition, the C-indices (standard deviation) of IPI and KPI were 0.580 (0.07) and 0.642 (0.07) for OS, and were 0.606 (0.06) and 0.606 (0.06) for PFS, respectively.

Discussion

We herein demonstrated that KPI might be a useful predictor of outcomes compared with the IPI in the cohort of JCOG0908, which was conducted to select promising induction regimen for upfront HDT with ASCT in patients with newly diagnosed DLBCL. The KPI had precise discrimination in both OS and PFS compared with the IPI in patients with DLBCL, even in youth-based cohort. Intriguingly, OS and PFS of patients with IPI-defined LI was inferior to those of patients with HI, and, moreover, PFS curve of IPI-defined LI mostly superimposed with that of IPI-defined H in this cohort of JCOG0908. One possible explanation of this discrepancy was that a certain number of favorable patients may be included in IPI-defined high risk group. Indeed, in our cohort, 23 of 46 IPI-defined HI or H patients were classified as LI according to KPI, while 5 out of 12 patients with IPI-defined LI were classified as HI or H according to KPI. Thus, the IPI might not work for these population appropriately. Such as change of the prognostic values of risk variables included in IPI by the addition of rituximab on CHOP was reported by the pivotal investigation by Sehn *et al*. which proposed the need of revised-IPI for DLBCL (4).

Several reasons are conceivable for the differences in risk classification between the IPI and the KPI. First, the assignment incremental scores to increased LDH level 'ULN to 3-fold to ULN, score 1' and 'over 3-fold to ULN, score 2' in KPI rather than the simple dichotomization by 'normal range' and 'over ULN' in IPI might allow us to distinguish high-risk patients more accurately. Recently, a refined categorization of LDH by the degree of elevation has been also shown to provide better prognostication of DLBCL in NCCN-IPI (5). Highly increase in serum LDH is associated with worse outcomes in DLBCL, however, those might not be well evaluated in IPI. Indeed, among 21 of 58 patients those presented the increase of LDH over 3-fold to ULN, 11 patients were classified H by KPI, while only five by IPI. Second, the prognostic value of decreased serum Alb below 3.5 g/dl is incorporated as a prognostic factor in KPI, but not in IPI. Hypoalbuminemia may represent systemic exhaustion due to tumor aggressiveness, inflammation, malnutrition and basic physical fitness, those all may contribute to treatment outcome (17,18).

Patient's age is generally well-known prognostic parameter for DLBCL included in the IPI risk factors. Because only approximately one-fourth of evaluable patients were over 61 years old in the specific cohort analyzed in this study, the prognostic value of age in this cohort may be less compared with that in real-world setting including all patients. Even apart from JCOG0908 cohort, the number of elderly patients continues to increase in an aging society and the patients' age distribution has been changed from that in 1993 when IPI was initially proposed. Also, the health status of the elderly patients has changed from that of approximately three decades ago. In fact, the KPI does not include the patient's age as an independent prognostic factor. Thus, prognostic value and cut-off threshold of age should be re-evaluated in DLBCL.

We demonstrated relatively favorable survival outcomes for higher risk DLBCL in JCOG0908. The difference in the survival outcome of KPI-defined H risk patients between JCOG0908 (3-year OS 61.5% and 3-year PFS 46.2%) and the previous study, which we proposed the KPI (3-year OS 33.3% and 3-year PFS 24.1%) might be due to the difference in patients' background, such as age and PS, and treatment strategies. To further validate the usefulness of KPI, it would be desired to investigate the prognostic value of KPI in elderly or transplant-ineligible patients with DLBCL.

There are some limitations in the current study, as the number of patients were limited, and patients analyzed were limited to higher

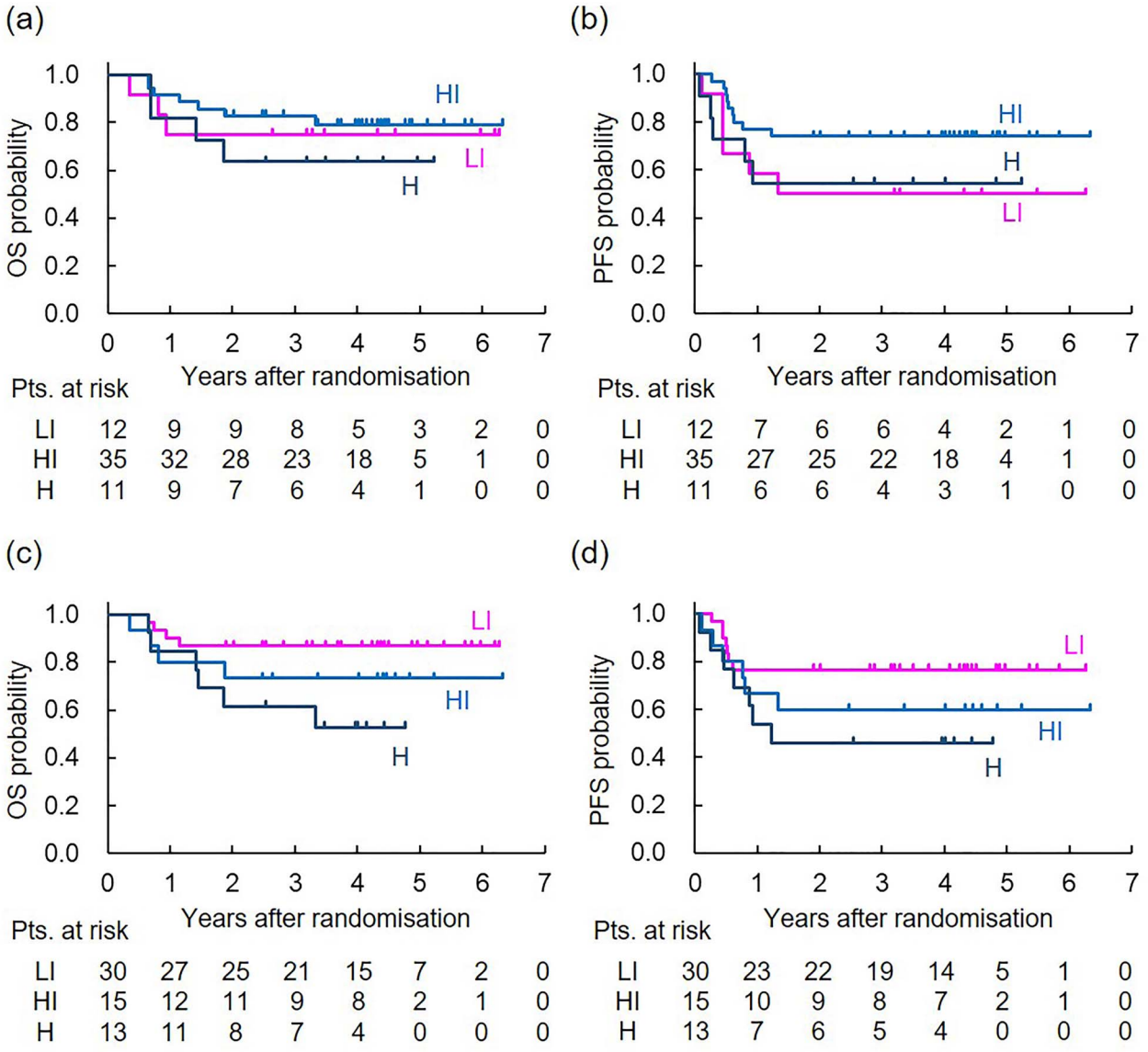

Figure 2. (a, b) Overall survival (a) and progression-free survival (b) according to the IPI. (c, d) Overall survival (c) and progression-free survival (d) according to the KPI.

risk by the aa-IPI. Therefore, we are presently planning the next analysis of JCOG clinical trials with larger sample size, including IPI-defined lower risk DLBCL patients treated with R-CHOP chemotherapy. Also, to establish the risk-adapted treatment selection, our data may provide information for the future planning of next clinical trial.

In conclusion, the KPI had a suitable predictive ability for the efficacy outcomes in patients with DLBCL treated with upfront HDT with ASCT. The KPI may represent a useful tool for further development of treatment strategy in such higher risk DLBCL patients.

Authorship contribution

T.K., K.Y., Y.K., J.K., D.M. and H.N. designed the research; R.M. analyzed data; T.K. and J.K. drafted the manuscript; K.Y., Y.K., R.M., K.M., S.N., J.K., D.M. and H.N. reviewed and approved the final version of the manuscript.

Supplementary material

Supplementary material can be found at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement

Kazuhito Yamamoto has received research funding from AbbVie, Astra-Zeneca, Bayer, Celgene, Chugai, Eisai, Gilead Sciences, IQIVA/Incyte, MSD, Mundipharma, Nippon Shinyaku, Novartis, Ono, Otsuka, Solasia Pharma, SymBio, Takeda, Yakult and Zenyaku; has received honoraria from AbbVie, ADC Therapeutics, Astra-Zeneca, Bristol-Myers Squibb, Celgene, Chugai, Daiichi Sankyo, Eisai, IQIVA/HUYA, Janssen, Kyowa Kirin, Meiji Seika Pharma, Micron, MSD, Mundipharma, Nippon Shinyaku, Novartis, Ono, Otsuka, Pfizer, Sanofi, Stemline Therapeutics, Sumitomo Dainippon, SymBio, Takeda and Zenyaku; and has received advisory/consultancy from Meiji Seika Pharma. Kana Miyazaki has received honoraria from Kyowa Kirin, and Astellas Pharma. Junya Kuroda has received research funding from Bristol–Myers Squibb, Sysmex, Celgene, Ono Pharmaceutical, Otsuka Pharmaceutical, Sanofi, Kyowa Kirin, Sanofi, Chugai Pharmaceutical, Eisai, Dainippon Sumitomo Pharma, Nippon Shinyaku, Takeda, Shionogi, Asahi Kasei, Daiichi Sankyo, MSD, Taiho Pharmaceutical and Abbvie; has received honoraria from Bristol–Myers Squibb, Janssen Pharmaceutical K.K, Celgene Corporation, Ono Pharmaceutical, Takeda, Sanofi, Kyowa Kirin, Chugai Pharmaceutical, Eisai, Astellas Pharma, Nippon Shinyaku, Dainippon Sumitomo Pharma, Symbio, Daiichi Sankyo, Fujimoto Pharmaceutical, Abbvie and Otsuka Pharmaceutical; and is a consultant of Janssen Pharmaceutical K.K, Celgene, Bristol-Myers Squibb, Sanofi and Abbvie. Dai Maruyama has received research funding from MSD, Celgene, Novartis Pharma, Mundipharma K.K, Janssen Pharmaceutical K.K, Ono Pharmaceutical, Chugai Pharmaceutical and Takeda; has received honoraria from Celgene, Mundipharma K.K, Janssen Pharmaceutical K.K, Chugai Pharmaceutical, Kyowa Kirin, Eisai and Takeda. Hirokazu Nagai has received research funding from Astra-Zeneca, Bayer, Zenyaku, Takeda, Chugai Pharmaceutical, Mundipharma K.K, SymBio and Celgene; has received honoraria from Takeda, Eisai, Chugai Pharmaceutical and Celgene. Others have no conflicts of interest to declare.

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