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ORIGINAL ARTICLE

Central nervous system relapse in patients with diffuse large B cell lymphoma: analysis of the risk factors and proposal of a new prognostic model

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Abstract Central nervous system (CNS) relapse in patients with diffuse large B cell lymphoma (DLBCL) is an uncommon event, and the outcome of patients with CNS relapse is poor. However, no reliable prediction models for CNS relapse have been developed. We retrospectively analyzed consecutive de novo DLBCL patients referred to our department between September 2004 and August 2015 and treated with R-CHOP or R-CHOP-like regimens. Of 413 patients analyzed in this study, a total of 27 patients (6.5 %) eventually developed CNS relapse. The 5-year probability of CNS relapse was 8.4 %. The median time from diagnosis of DLBCL to CNS relapse was 15 months, and the median survival after CNS relapse was 7 months. In univariate analysis, the risk factors significantly associated with CNS relapse were Ann Arbor stage 3 or 4, albumin level <3.2 mg/L, number of extranodal sites >1, and involvement of retroperitoneal lymph node. We developed a new prognostic model consisting of these four factors. The 5-year probability of CNS relapse was significantly higher in patients with at least three of these four factors than in those with two or fewer factors (26.4 vs. 3.0 %, $P < 0.001$). Using this model, we evaluated the incidence and the risk factors of CNS relapse in DLBCL patients. The new risk model consisting of the four factors demonstrated good risk stratification for CNS relapse, and could help to identify high-risk patients for whom CNS prophylaxis is warranted.

Keywords Diffuse large B cell lymphoma · Central nervous system relapse · Risk factor · Prognostic model

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subgroup of non-Hodgkin lymphoma [1]. The survival outcome of patients with DLBCL has improved dramatically with addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy [2–5].

Central nervous system (CNS) relapse in patients with DLBCL is an uncommon event and carries an extremely poor prognosis even in the rituximab era, with median survival after CNS relapse of less than 6 months [6–10]. Although CNS-directed prophylaxis is often administered in attempt to reduce the incidence of CNS relapse, this treatment may increase the toxicities of the systemic chemotherapy. There is a lack of consensus about which patients should receive CNS-directed prophylaxis, as well as the actual effectiveness of prophylaxis in the rituximab era.

There are several risk models for predicting CNS relapse, including models proposed by Hollender et al. in the pre-rituximab era [11] and by Schmitz et al. in the rituximab era [12]. Although both models can effectively select high-risk patients to a certain extent, the prognostic values have not been extensively validated. Furthermore, the incidence of CNS relapse in the high-risk patients defined by these models was not so high that CNS prophylaxis was warranted in all of these patients. Therefore, a new model is needed to more effectively identify patients at high risk for CNS relapse.

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In this retrospective study, we evaluated the incidence and the risk factors of CNS relapse in DLBCL patients in the rituximab era using a database of our hospital. Additionally, we proposed a new prognostic model for CNS relapse and compared the prognostic value of this model with that of the previously proposed models.

Methods

Patients

We reviewed the records of 472 consecutive patients with de novo DLBCL who were newly diagnosed between September 2004 and August 2015 and treated in our hospital. The data of patients who were treated with R-CHOP or R-CHOP-like regimen were analyzed. We excluded patients with primary CNS lymphoma, intravascular B cell lymphoma, and with CNS involvement at diagnosis from this analysis. Patients were also excluded if they had human immunodeficiency virus-associated lymphoma or transformed lymphoma from a prior indolent B cell lymphoma. None of these patients had previously been treated for DLBCL.

Evaluation of the CNS at diagnosis by computed tomography/magnetic resonance imaging or by lumbar puncture with cerebrospinal fluid analysis was carried out at the discretion of the treating physician. Diagnosis of CNS relapse was established by the presence of intracranial or spinal masses detected by neurological imaging (parenchymal type), or by malignant cells detected by cerebrospinal fluid cytology (leptomeningeal type).

The pathological diagnosis was made according to the WHO 2008 classification. Clinical staging was performed according to the Ann Arbor classification. Computed tomography (CT) scans were performed in all patients and positron emission tomography (PET) scans were performed in some of the patients for staging. Performance status (PS) was evaluated based on Eastern Cooperative Oncology Group criteria. The International Prognostic Index (IPI) and the National Comprehensive Cancer Network (NCCN)-IPI were calculated based on age, serum lactate dehydrogenase (LDH), PS, Ann Arbor stage, and extranodal involvements at diagnosis [13, 14]. The clinical tumor response was assessed by CT and/or PET/CT scanning after completion of the initial therapy according to the International Workshop Criteria [15].

This study was approved by the institutional ethics review boards of our hospital and informed consent for retrospective analysis was obtained from all patients.

Treatment

All patients in this study were treated with at least once cycle of an R-CHOP or an R-THP-COP. In the R-THP-COP

regimen, terahydropyranyladriamycin was used instead of doxorubicin [16]. CNS prophylaxis was carried out in 62 patients, who were considered as high risk for CNS relapse because of extranodal involvements such as testis, breast, paranasal sinuses, or bone marrow. These patients received intrathecal (IT) injection of methotrexate (MTX) with or without cytarabine (Ara-C) at least once. No patient received systemic MTX for CNS prophylaxis.

Prognostic models for CNS relapse

The risk of CNS relapse was stratified according to the new risk model, as well as according to previous models. The model by Hollender et al. was composed of LDH >institutional upper limit of normal, albumin level <3.2 mg/L, age >60 years, retroperitoneal lymph node involvement, and number of extranodal sites >1 [11]. Based on this model, we stratified the patients into two groups: a low-risk (0–3 factors) and a high-risk (4–5 factors) group. The model by Schmitz et al. was based on the five IPI factors and kidney and/or adrenal grand involvement, assigning patients into low-risk (0–1 factor), intermediate-risk (2–3 factors), or high-risk (4–6 factors) groups [12]. These risk models are compared in Table 1.

Statistical analysis

Time to CNS relapse (TTCNS) was defined as the period from the date of diagnosis of DLBCL to the date of CNS relapse. Patients who died without CNS relapse were censored in analysis of TTCNS. Overall survival (OS) was defined as the period from the date of diagnosis of DLBCL (or from the date of CNS relapse, where applicable) to the date of last follow-up or death from any cause. TTCNS and OS were estimated using the Kaplan-Meier method. Differences between survival curves were tested for significance using the log-rank test. Baseline characteristics of the patients with and without CNS relapse were compared using Fisher's exact test for categorical data. All P values were two sided, and P values of 0.05 or less were considered significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [17].

Results

Patient characteristics

We analyzed the data of 413 patients who met the inclusion criteria. The median age was 68 years (range, 27–97 years).

Table 1 Comparison of the risk models for CNS relapse

Hollender et al. [11]		Schmitz et al. [12]		This study	
Extranodal sites >1		Extranodal sites >1		Extranodal sites >1	
Albumin <3.5 mg/dL				Albumin <3.5 mg/dL	
Retroperitoneal lymph node involvement				Retroperitoneal lymph node involvement	
		Stage 3 or 4		Stage 3 or 4	
Age >60		Age >60			
Elevated LDH		Elevated LDH			
		PS >1			
		Kidney or adrenal grand			
Risk group		Risk group		Risk group	
Low risk	0–3	Low risk	0–1	Low risk	0–2
High risk	4–5	Intermediate risk	2–3	High risk	3–4
		High risk	4–6		

The median number of cycles of chemotherapy was 6 (range, 1–8). The median follow-up time of surviving patients was 38 months. A complete response was achieved in 300 patients (72.6 %), a partial response was achieved in 98 patients (23.7 %), and 15 patients (3.6 %) showed progressive disease after the initial therapy. The characteristics of the patients with and without CNS relapse are presented in Table 2. Overall, baseline characteristics were similar between the two groups, although there were a greater proportion of patients in the CNS relapse group with advanced stage, low serum albumin level, the presence of extranodal diseases, involvement of retroperitoneal lymph node and bone marrow, and high-intermediate (HI)- and high (H)-risk patients by the IPI and the NCCN-IPI. Fourteen patients (22.6 %) in the CNS relapse group and 48 patients (13.9 %) in the non-CNS relapse group received IT prophylaxis, with no significant difference between the two groups.

CNS relapse

In total, 27 patients (6.5 %) eventually developed CNS relapse. The 5-year probability of CNS relapse was 8.4 % (95 % confidence interval, 5.6–12.4 %). The median time from the diagnosis of DLBCL to CNS relapse was 15 months (Fig. 1). More than half of the patients with CNS relapse had leptomeningeal diseases (59.3 %), while nine had parenchymal diseases (33.3 %) and two had both (7.4 %). Sixteen patients (59.3 %) developed isolated CNS relapse and 11 (40.7 %) had CNS relapse in the context of systemic relapse. The median survival after CNS relapse was 7 months (Fig. 2).

Risk factors for CNS relapse

The influence of the following variables on TTCNS was evaluated: age >60 years; male sex; the presence of B symptoms; PS >1; Ann Arbor stage 3 or 4; LDH >institutional upper limit

of normal; albumin level <3.2 mg/L; number of extranodal sites >1; involvement of testes, breast, paranasal sinus, kidneys, adrenal glands, retroperitoneal lymph node, and bone marrow; high-intermediate (HI) or high (H) risk by IPI and NCCN-IPI; and the administration of IT prophylaxis. Univariate analysis results are shown in Table 3. The following risk factors were significantly associated with CNS relapse: Ann Arbor stage, albumin level, number of extranodal sites, involvement of retroperitoneal lymph node, and HI or H risk by IPI and NCCN-IPI.

New risk model for CNS relapse

We developed a new prognostic model consisting of four factors: Ann Arbor stage 3 or 4, albumin level <3.2 mg/L, number of extranodal sites >1, and involvement of retroperitoneal lymph node. Two distinct risk groups were formed based on Kaplan-Meier survival curves: a low-risk group with 0–2 factors ($n = 301$, 72.9 %); and a high-risk group with 3–4 factors ($n = 112$, 27.1 %) (Table 1). This model distinguished two groups with a significantly different relapse rate; the 5-year probability of CNS relapse was 3.0 and 26.4 % for patients in the low- and high-risk groups, respectively ($P < 0.001$) (Fig. 3). We also adapted this model to the analysis of isolated CNS relapse. The 5-year probability of isolated CNS relapse was 2.5 and 11.7 % for patients in the low- and high-risk groups, respectively ($P < 0.001$) (Fig. 4).

Comparison of the prognostic values of the new model with those of other models

We compared the prognostic powers of the new model for predicting CNS relapse with those of the models reported by Hollender and by Schmitz [11, 12]. The estimated 5-year probability of CNS relapse in the

Table 2 Characteristics of the study patients with or without central nervous system relapse

| Characteristic	Overall	CNS relapse (+)	CNS relapse (−)	P value
Number of patients	413	27	386	
Age median (years)	68	67	68	0.51
>60	300 (72.6 %)	18 (66.7 %)	282 (73.1 %)	
Sex (male)	229 (55.4 %)	19 (70.4 %)	210 (54.4 %)	0.11
B symptom (+)	96 (23.2 %)	8 (29.6 %)	88 (22.8 %)	0.48
Performance status (>1)	89 (21.5 %)	7 (25.9 %)	82 (21.2 %)	0.63
Ann Arbor stage (3 or 4)	207 (50.1 %)	23 (85.2 %)	184 (47.7 %)	<0.001
LDH (>normal upper limit)	226 (54.7 %)	19 (70.4 %)	207 (53.6 %)	0.11
Albumin (<3.5 mg/dL)	155 (37.5 %)	17 (63.0 %)	138 (35.8 %)	0.007
Extranodal diseases (>1)	107 (25.9 %)	15 (55.6 %)	92 (23.8 %)	0.001
Testes	12 (2.9 %)	0 (0 %)	12 (3.1 %)	1.00
Breasts	13 (3.1 %)	1 (3.7 %)	12 (3.1 %)	0.59
Paranasal sinus	20 (4.8 %)	3 (11.1 %)	17 (4.4 %)	0.14
Kidneys	9 (2.2 %)	0 (0 %)	9 (2.3 %)	1.0
Adrenal glands	15 (3.6 %)	2 (7.4 %)	13 (3.4 %)	0.26
Retroperitoneal lymph node	153 (37.0 %)	19 (70.4 %)	134 (34.7 %)	<0.001
Bone marrow	62 (15.0 %)	8 (29.6 %)	54 (14.2 %)	0.047
IPI (HI or H)	159 (38.5 %)	18 (66.7 %)	141 (36.5 %)	0.003
NCCN-IPI (HI or H)	224 (54.2 %)	20 (74.1 %)	204 (52.8 %)	0.044
IT prophylaxis	62 (15.0 %)	14 (22.6 %)	48 (13.9 %)	0.086
R-CHOP regimen	346 (83.8 %)	23 (85.2 %)	323 (83.7 %)	1.00
Cycles of chemotherapy (median)	6 (range, 1–8)	6 (range, 1–8)	6 (range, 1–8)	0.60
Response (CR)	300 (72.6 %)	17 (63.0 %)	283 (73.3 %)	0.27

CNS central nervous system, *LDH* lactate dehydrogenase, *IPI* International Prognostic Index, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *HI* high-intermediate risk, *H* high risk, *IT* intrathecal, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *CR* complete response

low-risk group of the new model was lower than that of the Hollender and Schmitz models (3.0 % vs. 5.6 and 3.5 %, respectively), whereas the 5-year probability of CNS relapse in the high-risk group of the new model was higher than that of the other models (26.4 % vs. 18.3 and 17.6 %, respectively) (Fig. 3).
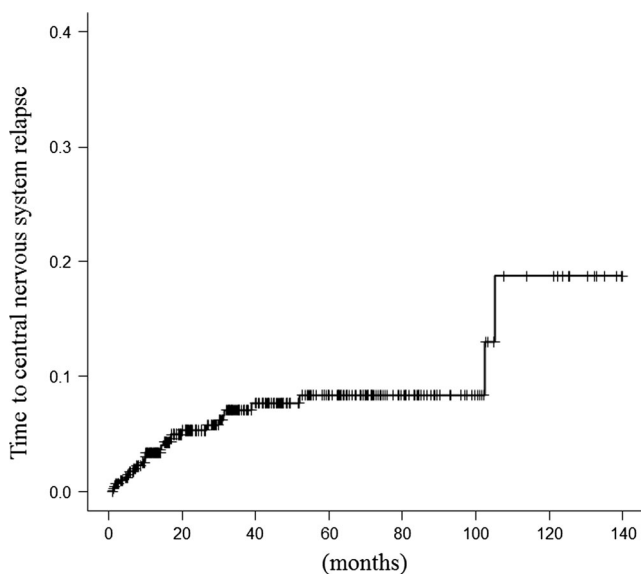
Fig. 1 Kaplan-Meier curve of time to central nervous system relapse in the entire cohort
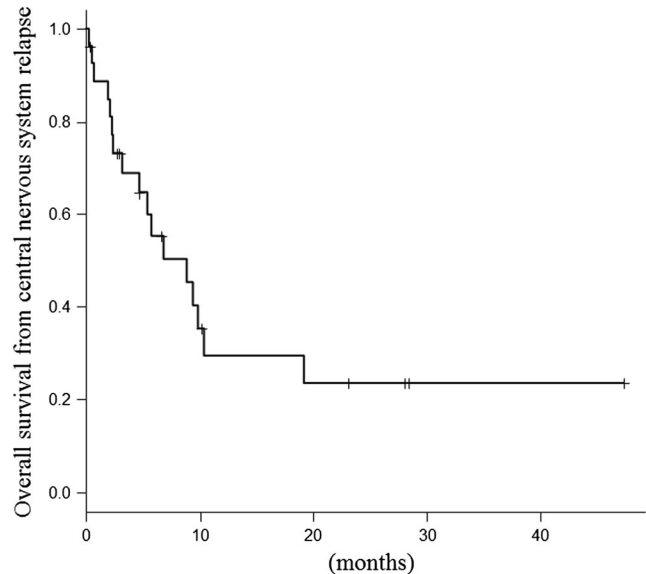
Fig. 2 Kaplan-Meier curve of overall survival after central nervous system relapse

Table 3 Univariate analysis of clinical factors for CNS relapse

	Univariate analysis	
	Hazard ratio (95 % CI)	P value
Age (>60)	0.83 (0.37–1.86)	0.66
Sex (male)	2.01 (0.88–4.59)	0.098
B symptom (+)	1.59 (0.69–3.63)	0.27
Performance status (>1)	1.74 (0.73–4.14)	0.21
Ann Arbor stage (3 or 4)	7.44 (2.56–21.64)	<0.001
LDH (>normal upper limit)	1.99 (0.78–5.04)	0.15
Albumin (<3.5 mg/dL)	3.81 (1.73–8.37)	<0.001
Extranodal diseases (>1)	5.24 (2.41–11.39)	<0.001
Testes[a]	Not analyzed	
Breasts	1.02 (0.14–7.51)	0.99
Paranasal sinus	2.26 (0.68–7.49)	0.18
Kidneys[a]	Not analyzed	
Adrenal glands	3.45 (0.82–14.91)	0.091
Retroperitoneal lymph node	4.96 (2.16–11.36)	<0.001
Bone marrow	3.15 (0.97–7.31)	0.054
IPI (HI or H)	5.65 (2.35–13.61)	<0.001
NCCN-IPI (HI or H)	3.24 (1.35–7.75)	0.008
IT prophylaxis (+)	0.85 (0.29–2.45)	0.76

CNS central nervous system, *CI* confidence interval, *LDH* lactate dehydrogenase, *IPI* International Prognostic Index, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *HI* high-intermediate risk, *H* high risk, *IT* intrathecal

[a] Because there were no CNS relapse among patients with testes and kidneys involvements, we did not analyze the effect of these factors

Discussion

In this study cohort, the incidence of CNS relapse was 8.4 %. Previous studies reported that the incidence of CNS relapse in DLBCL patients was between 1.1 and 10.4 % [6–8, 11, 18–26]. This wide range in the reported rate may be due to the heterogeneity of the study populations, associated risk factors,
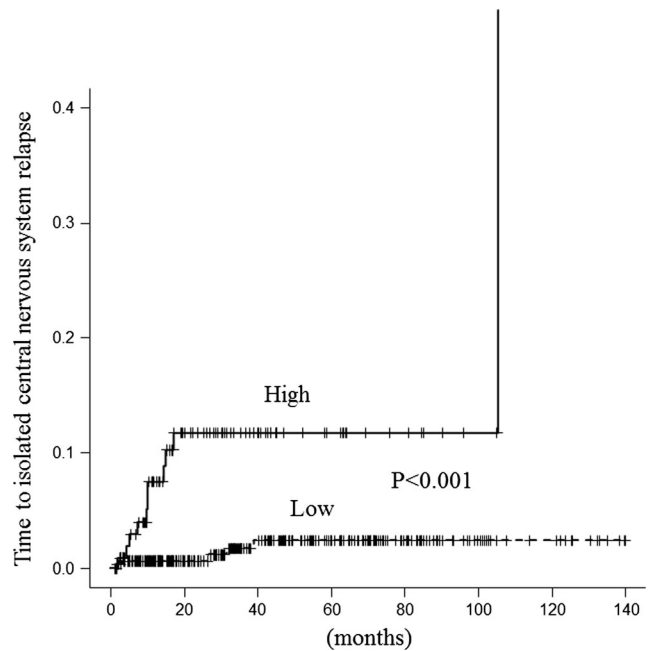
Fig. 4 Kaplan-Meier curve of time to isolated central nervous system relapse according to the new risk model

accuracy of diagnostic procedures, and the type of systemic therapy and CNS-directed prophylaxis.

There is controversy regarding whether rituximab has a protective effect against CNS relapse or not. The randomized prospective RICOVER-60 trial of 1222 patients with aggressive B cell lymphoma on CHOP-14 with or without rituximab suggested that rituximab decreased the risk of CNS relapse; the relative risk decreased to 0.58 (95 % CI 0.3–1.0, *P* = 0.046) [7]. On the other hand, a study conducted by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) on 399 elderly patients with DLBCL treated with CHOP with or without rituximab could not demonstrate any effect of rituximab on the risk of CNS relapse [6]. Conflicting results have been reported from several other studies with some demonstrating a reduction in risk [8, 25, 27, 28] and others demonstrating no
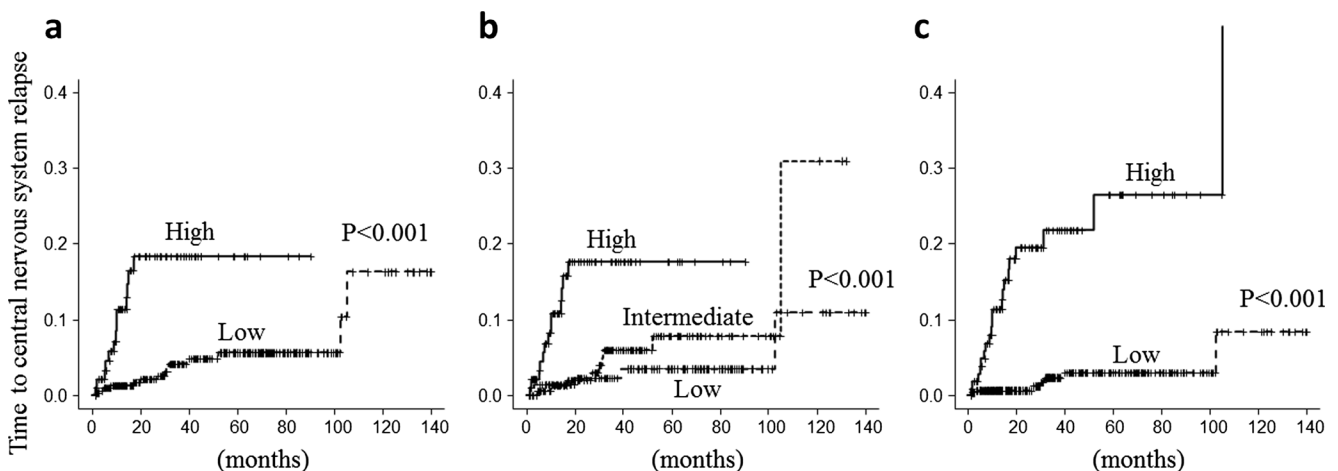
Fig. 3 Kaplan-Meier curves of time to central nervous system relapse according to Hollender et al. (**a**), Schmitz et al. (**b**), and the new risk model (**c**)

reduction [9, 20, 21, 29]. As reported in a recent meta-analysis, the effect of rituximab on CNS relapse remains controversial [30, 31].

IT chemotherapy, including MTX, Ara-C, and steroids, has been largely used as a strategy for CNS prophylaxis. The RICOVER-60 trial, described above, showed that IT MTX failed to reduce the risk of CNS relapse in elderly patients with DLBCL treated with R-CHOP14. Further subgroup analysis suggested that IT prophylaxis may benefit patients treated without rituximab, but also suggested that this benefit was lost when rituximab was added to CHOP [7]. Other studies in the rituximab era also did not demonstrate a significant benefit of IT MTX [8, 21, 28, 32]. However, IT MTX is an important part of the treatment of patients with primary testicular DLBCL [33]. Due to the poor penetration of IT chemotherapy, it is unlikely to have a protective effect on parenchymal relapses. As an alternative method of reducing CNS relapse, CNS-penetrating doses of antimetabolites such as MTX and Ara-C have been recently used to prevent CNS relapse. Although there have been several studies that support the efficacy of systemic MTX in the rituximab era [10, 27, 34, 35], the optimal dose, infusion rate, number of cycles, and the need for concomitant IT chemotherapy remain unclear.

Even though several studies have attempted to identify patients with a high rate of CNS relapse, there remains no consensus regarding how to define high-risk patients. The involvement of many specific anatomic sites has been proposed as predictors of increased risk of CNS relapse. In particular, testicular involvement is consistently correlated with a high relapse rate [36]. Breast, kidney, adrenal glands, paranasal sinuses, epidural space, bone, and bone marrow involvement have also been reported as high-risk sites [37]. Other clinical factors, such as elevated LDH level and more than one extranodal involvement, have been identified as risk factors [6, 7, 25, 29]. However, other studies have demonstrated no significant increase in CNS relapse in patients with these clinical factors [8, 9, 20, 21, 38], and no consistent conclusion regarding this matter has yet been reached.

Several biological risk factors associated with CNS relapse have been reported. Patients harboring *MYC* gene rearrangement or a combination of *MYC* and *BCL2* translocations have a significantly higher risk of CNS relapse, ranging between 9 and 50 % [39–45]. A recent study suggested that dual expression of MYC and BCL2 is associated with an increased risk of CNS relapse, with an estimated 2-year risk of 9.7 % [46]. Patients with DLBCL whose tumors are CD5 positive have been reported to have increased risk of CNS relapse; the 2-year CNS relapse rate was 12.7 % [47].

Although no single risk factor has been reported to have sufficient predictive value, specific combinations of such factors are expected to be more highly associated with the risk of CNS relapse. Hollender et al. analyzed 1220 patients with high grade non-Hodgkin lymphoma and proposed a prognostic model composed of LDH level, albumin level, age, retroperitoneal lymph node involvement, and number of extranodal sites >1. The risk of CNS relapse was 6.2 % or less at 5 years with up to three of these risk factors, whereas it rose to 25.3 % with four of these factors and to 32.7 % with all of the factors [11]. Schmitz et al. analyzed 2164 patients with DLBCL in the German High-Grade Lymphoma Study Group (DSHNHL) prospective study and identified IPI factors and kidney and/or adrenal grand involvement as independent risk factors for CNS relapse. Low- (0–1 factor), intermediate- (2–3 factors), and high-risk (4–6 factors) groups had a 2-year actuarial CNS relapse rate of 0.6, 4.1, and 17.0 %, respectively [12]. Although those two risk models could distinguish two or three patient groups with significantly different relapse rates, the new model proposed in this study demonstrated better risk stratification than those models.

HI or H risk by IPI, which was not included in the new model, was also associated with CNS relapse (Table 3). We investigated the effect of the model consisting of the five factors, HI or H risk by IPI and the four factors in the new risk model. Two distinct risk groups were formed based on Kaplan-Meier survival curves: a low-risk group with 0–3 factors ($n = 316$, 76.5 %); and a high-risk group with 4–5 factors ($n = 97$, 23.5 %). The 5-year probability of CNS relapse was 5.4 and 18.8 % for patients in the low- and high-risk groups, respectively ($P < 0.001$) (Fig. 5). Although this model could also stratify the risk of CNS relapse, the prognostic value of the four-factor model was suggested to be better than that of this five-factor model.

There were some limitations to this study. First, this was a retrospective study conducted in a single institute, and had some biases. In particular, there were inconsistencies in the
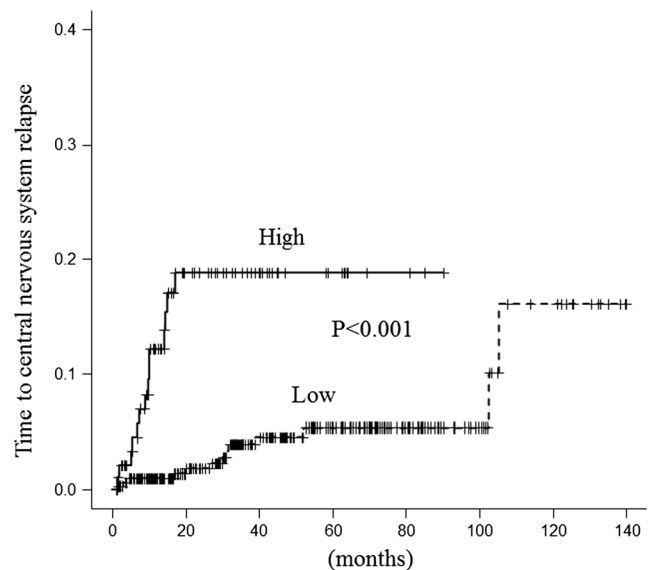
Fig. 5 Kaplan-Meier curves of time to central nervous system relapse according to the model consisting of the five factors, HI or H risk by IPI, and the four factors in the new risk model

indication, timing, dose, and number of times of CNS prophylaxis. Although the efficacy of IT prophylaxis was not proven in this study, this may be due to the small number of the patients with CNS relapse and it is difficult to estimate whether IT prophylaxis had some impact on the risk of CNS relapse. Second, the prognostic influences of immunohistochemical markers or biologic markers such as translocation involving *MYC* and *BCL2* were not taken into account. Third, there was a small number of CNS relapses and the analysis of each risk factor had poor statistical power. Among the involved sites, involvement of retroperitoneal lymph node was the only factor to reach statistical significance for CNS relapse. This was likely to be because of the larger number of patients with retroperitoneal lymph node involvement. Clinicians should still consider possible site-specific indications for CNS prophylaxis in addition to the new prognostic model. Finally, this new model was derived from a dataset from a single institution, and needs to be validated using independent datasets.

Conclusion

We analyzed the incidence and the risk factors of CNS relapse in patients with DLBCL in the rituximab era. A new prognostic model consisting of the four factors: Ann Arbor stage 3 or 4, albumin level <3.2 mg/L, number of extranodal sites >1, and involvement of retroperitoneal lymph node, demonstrated better risk stratification than the previously reported models. This model may help to identify high-risk patients who would benefit from CNS-directed prophylaxis.

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