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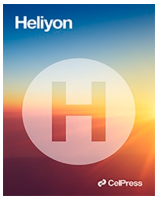

Research article

Predicting central nervous system relapse in primary breast diffuse large B-cell lymphoma using the stage-modified IPI score: A retrospective cohort study

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ABSTRACT

Objective: The existing Central Nervous System-International Prognostic Index (CNS-IPI) provides insufficient guidance for predicting central nervous system (CNS) relapse in individuals with primary breast diffuse large B-cell lymphoma (DLBCL). This retrospective cohort study sought to examine the potential of the stage-modified IPI in predicting CNS relapse within this specific patient population.

Patients and methods: We examined the baseline characteristics of 76 consecutive patients diagnosed with primary breast DLBCL, calculating the stage-modified IPI score for each individual. Utilizing a competing risk regression (CRR) model, we conducted both univariate and multivariate analyses to explore the relationship between potential prognostic factors and the occurrence of CNS relapse.

Results: In our cohort, the rates of CNS disease at 2 and 5 years since the diagnosis of primary breast DLBCL are 3.9% and 7.8%, respectively. Among patients experiencing CNS relapse, 80% presented with a parenchymal brain mass. Individuals with a high stage-modified IPI score (1–3 points) had a significantly higher incidence of CNS relapse ($p = 0.031$), a shorter time from the initial diagnosis of primary breast DLBCL to the first CNS relapse ($p = 0.010$), as well as relapse at any site ($p = 0.012$), compared to those with a low score (0 points). Univariate analysis identified stage (Hazard Ratio (HR): 4.098, $p = 0.024$), stage-modified IPI score (HR: 11.582, $p = 0.012$), and radiation therapy (HR: 5.784, $p = 0.026$) as significant risk factors. In multivariate analysis, in addition to radiation therapy (HR: 7.258, $p = 0.012$), the stage-modified IPI score (1–3 points versus 0 points) emerged as an independent and reliable predictor for CNS relapse (HR: 12.945, $p = 0.016$).

Conclusion: Our study underscores the significance of stage-modified IPI scores in predicting CNS relapse for patients with primary breast DLBCL. Validation of these findings through further research is essential, along with exploring potential prevention and intervention approaches.

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1. Introduction

Primary breast diffuse large B-cell lymphoma (DLBCL) represents a distinctive form of lymphoma primarily localized in one or both breasts, potentially involving regional lymph nodes such as ipsilateral axillary and/or supraclavicular lymph nodes [1]. Despite its primary breast origin, patients with this condition often face a heightened risk of central nervous system (CNS) relapse, with rates reaching up to 16% at the 10-year mark [2–5]. This complication is associated with an exceedingly poor prognosis in DLBCL [4–6]. Consequently, there is significant interest in identifying high-risk patients to tailor prophylactic therapies, with the goal of improving outcomes for DLBCL patients [2–4,7].

The CNS-International Prognostic Index (CNS-IPI) score has been identified as a robust and highly reproducible tool for assessing the risk of CNS relapse in DLBCL patients [8–10]. However, its application to primary breast DLBCL cases typically assigns most patients to the low-risk group, with none falling into the high-risk category [11]. Consequently, the CNS-IPI offers limited utility in predicting CNS recurrence in primary breast DLBCL. As a result, a reliable CNS recurrence prediction model based on available clinical data for primary breast DLBCL in routine clinical practice is still lacking. In our earlier research, we identified that both the stage-modified IPI score and CNS relapse independently influence the survival of patients with primary breast DLBCL [5]. Furthermore, the IPI score has proven useful in predicting survival in DLBCL, sharing remarkably similar clinical parameters with the CNS-IPI score. Meanwhile, the stage-modified IPI score serves as an independent prognostic factor in cases of primary breast DLBCL [5]. Indeed, individuals with stage IIE disease and higher IPI scores demonstrated an increased likelihood of developing CNS relapse in primary breast DLBCL [3]. This prompts us to investigate whether the stage-modified IPI score can similarly identify a high-risk group susceptible to CNS relapse among patients with primary breast DLBCL.

As primary breast DLBCL represents a rare form of non-Hodgkin lymphoma, we leveraged our previous retrospective cohort to conduct an analysis using the competing risk regression (CRR) model to examine the association of clinical predictors with the time to CNS relapse. The insights gleaned from identifying these clinical predictors for CNS relapse can offer valuable guidance and recommendations for managing primary breast DLBCL.

2. Materials and methods

2.1. Participants and study design

We retrospectively reviewed a consecutive cohort of 76 patients who received a diagnosis of primary breast DLBCL at Fudan University Shanghai Cancer Center (FUSCC) between February 1997 and July 2018.The diagnosis and classification of DLBCL were determined by at least one pathologist who assessed the tissue's histology and interpreted the pattern of immunohistochemical markers, including Cluster of Differentiation 20 (CD20), Paired Box 5 (PAX5), and others [12]. This study was approved by the Institutional Review Board of the FUSCC (ZRB1612167-18) and carried out in accordance with relevant guidelines and regulations. The informed consent was obtained from all subjects and/or their legal guardian(s). Demographic information, tumor characteristics, diagnostic test results, administered treatments, and clinical outcomes were extracted from electronic medical records, as previously described [12,13]. CNS relapse was confirmed through imaging and pathological studies or cytology of cerebrospinal fluid. The primary outcome of interest was the time from the initial diagnosis of primary breast DLBCL to the first documented of CNS relapse, the date of the last follow-up, or October 01, 2021. In this study, 5 patients (6.6%) were considered lost to follow-up if their previous visit occurred more than 12 months before the end of the study.

The Ann Arbor system was applied for staging procedures [3,14]. In our cohort analysis, no instances of bilateral breast involvement were identified. The stage-modified IPI score [3,15,16] and germinal center B-cell-like (GCB) and non-GCB subtypes of DLBCL by Hans criteria [17] were determined using all the available information. Consistent with prior studies [12,15], the stage-modified IPI score was calculated based on the cumulative count of high-risk factors for each patient. These factors include age greater than 60 years, stage II disease (with involvement of nearby regional lymph nodes), elevated serum LDH concentration, and decreased Eastern Cooperative Oncology Group (ECOG) performance status. Response assessment was performed according to the International Working Group response criteria [3,18]. In this study, we defined relapse as lymphoma recurs after a period of complete remission, while the one that does not or partially respond to first-line chemotherapy is called refractory disease. Body Mass Index (BMI) is calculated by a person's weight in kilograms divided by the square of height in meters [19]. The time of initial diagnosis of primary breast DLBCL to a confirmed lymphoma lesion in the CNS was referred to CNS relapse-free survival.

2.2. Statistical analysis

All statistical analyses were performed using STATA version 16.0 (StataCorp LP, College Station, TX) and the Extreme Smart Analysis platform (https://www.xsmartanalysis.com/), with significance set at the 5% level. The Kruskal-Wallis H test was utilized for comparing multiple groups. A *t*-test was applied to compare the means of two given samples, and the chi-square test was employed for categorical variables. Variables with a missing rate exceeding 5% were excluded from the multivariate analysis. Time to CNS relapse was calculated from the date of initial diagnosis of primary breast DLBCL to the first documented date of CNS relapse. Associations between patient characteristics, which passed mediation analysis [20], and CNS relapse time were analyzed using a CRR analysis based on Fine and Gray's sub-hazard ratios (HRs) with 95% confidence interval (95% CI) [21]. In this analysis, CNS relapse-free death was defined as the competing event. Due to the small sample sizes and limited events, we employed resampling techniques using

bootstrapping, implemented with the R Package 'bootstrap.'. The Fine and Gray method was used to construct competing risk curves, and Gray's test was employed to calculate p-values for comparing cumulative incidence curves.

3. Results

By stratifying with the stage-modified IPI score, baseline characteristics of patients with primary breast DLBCL are summarized in Table 1. In our cohort, all patients were administered first-line chemotherapy regimens, primarily cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based or similar. Most of patients (73.6%) received chemotherapy combined with rituximab. Most of the characteristics were comparable, except for age and LDH levels. Nevertheless, it's worth noting that all these variables were taken into account when calculating the stage-modified IPI score. The occurrence of CNS relapse was significantly higher in the group with a high stage-modified IPI score (1–3 points) compared to the group with a low stage-modified IPI score (0 points) ($p = 0.031$). Notably, the time from the initial diagnosis of primary breast DLBCL to the first CNS relapse or progression-free survival (PFS) for relapse in any site also showed a significant gradual decrease trend with the stage-modified score ($p = 0.010$ and $p = 0.012$, respectively). Among the patients experiencing CNS relapse, 80% exhibited a parenchymal mass in the brain (Supplemental Table 1). Most cases with secondary CNS relapse have a non-GCB subtype of DLBCL. Notably, only one patient (10%) had no identified risk factors when the stage-modified IPI was applied, whereas 40% of cases exhibited no risk factors according to the CNS-IPI (Supplemental Table 1). Indeed, the 2-year and 5-year rates of CNS disease since the diagnosis of primary breast DLBCL are 3.9% (3 out of 76) and 7.8% (6 out of 76), respectively (Supplemental Table 1). Interestingly, one patient experienced three separate instances of CNS relapse.

Table 2 provides a summary of univariate analyses for the association between candidate prognostic factors and the time to CNS relapse using the CRR model. The variables of age, tumor size, non-GCB subtype, hepatitis B surface antigen (HBsAg) status, refractory disease, LDH, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) level were not found to be significant prognostic factors for CNS relapse in our cohort. Additionally, no difference was observed in the incidence of CNS relapse between treatment with or without rituximab, intrathecal injection, and breast surgery.

According to the CRR model, the significant risk factors for CNS relapse were stage (HR: 4.098, 95% CI 1.202 to 13.975, $p = 0.024$), stage-modified IPI score (HR: 11.582, 95% CI 1.716 to 78.189, $p = 0.012$), and radiation therapy (HR: 5.784, 95% CI 1.231 to 27.178, $p = 0.026$). In multivariate analysis, except for radiation therapy (HR: 7.258, 95% CI 1.534 to 34.344, $p = 0.012$), the stage-modified IPI score (HR: 12.945, 95% CI 1.606 to 104.375, $p = 0.016$) with a significant bootstrap 95% CI (1.745–40846613) demonstrated a

Table 1
Characteristics of patients with primary breast DLBCL.

	Stage-modified IPI score			
Characters	0	1	2–3	*P* value
N	37	31	8	/
Age, median [IQR]	48.0 [40.0,54.0]	54.0 [41.0,64.0]	64.0 [61.0,70.0]	**0.003**
≥ 60 year-of-old, n (%)	0 (0.0)	14 (45.2)	6 (75.0)	<0.001
Female, n (%)	37 (100.0)	30 (96.8)	8 (100.0)	0.484
BMI, mean (SD)	23.4 (3.5)	23.8 (2.6)	24.7 (3.2)	0.577
≥ 25, n (%)	9 (24.3)	12 (38.7)	4 (50.0)	0.251
ECOG score ≥2, n (%)	0 (0.0)	1 (3.2)	0 (0.0)	0.484
Tumor size ≥ 50 mm in diameter	6 (18.8)	6 (21.4)	2 (25.0)	0.917
Stage				<0.001
Stage I	37 (100.0)	18 (58.1)	0 (0.0)	
Stage IIE	0 (0.0)	13 (41.9)	8(100.0)	
Non-GCB	31 (86.1)	28 (93.3)	7 (77.8)	0.449
WBC count (10^9/l), mean (SD)	5.5 (1.62)	5.6 (1.57)	5.0 (1.06)	0.569
NLR, median [IQR]	1.7 [1.5, 2.5]	1.6 [1.3, 2.2]	2.5 [1.4, 2.7]	0.388
PLR, median [IQR]	214.0 [179.0,270.0]	210.0 [174.0,248.0]	196.0 [172.0,201.0]	0.440
LDH (IU/L), median [IQR]	176.0 [152.0,196.0]	181.0 [151.0,198.0]	221.0 [200.0,250.0]	**0.040**
≥ 250 IU/L, n (%)	0 (0.0)	3 (9.7)	3 (37.5)	<0.001
HBsAg positive, n (%)	5 (13.5)	3 (9.7)	1 (12.5)	0.886
Breast Surgery, n (%)	29 (78.4)	21 (67.7)	3 (37.5)	0.07
Rituximab exposure, n (%)	25 (67.6)	25 (80.6)	6 (75.0)	0.473
Intrathecal injection, n (%)	5 (13.5)	6 (19.4)	3 (37.5)	0.280
Refractory disease, n (%)	1 (2.7)	5 (16.1)	1 (12.5)	0.153
Radiation therapy, n (%)	16 (43.2)	12 (38.7)	3 (37.5)	0.912
CNS relapse, n (%)	1 (2.7)	7 (22.6)	2 (25.0)	**0.031**
Time to CNS relapse[a](months), median [IQR]	92.4 [66.1124.3]	68.6 [48.9,91.3]	53.8 [32.4,60.9]	**0.010**
PFS (months), median [IQR]	84.4 [60.9104.5]	67.8 [44.5,80.3]	42.8 [32.4,53.8]	**0.012**

Note: BMI, body mass index; CNS, central nervous system; CI, confidence intervals; DLBCL, diffuse large B-cell lymphoma; ECOG, eastern cooperative oncology group; GCB, germinal center B-cell like; IQR, interquartile range; IPI, international prognostic index; HBsAg, hepatitis B surface antigen; NLR, neutrophil-lymphocyte Ratio; LDH, lactate dehydrogenase; PFS, progression-free survival; PLR, platelet-lymphocyte ratio; UNL. Upper Normal Limit; WBC, white blood cell; SD, standard deviation.

[a] The time from the initial diagnosis of primary breast DLBCL to the first documented occurrence of CNS relapse.

Table 2
Univariate analysis of association between candidate risk factors and the time to CNS relapse.

		Univariate analysis		
Candidate prognostic factors	Comparison	HR	95% CI	P value
Age group	>60 versus ≤60	1.418	0.361 to 5.565	0.617
BMI	BMI ≥25 versus <25	0.896	0.230 to 3.486	0.874
Tumor size	≥50 mm versus <50 mm	1.423	0.249 to 8.125	0.691
Stage	Stage IIE versus I	4.098	1.202 to 13.975	**0.024**
Non-GCB	Positive versus negative	0.638	0.141 to 2.882	0.560
WBC count (10^9/l)	≥5.5 versus <5.5	0.988	0.279 to 3.502	0.986
NLR	≥1.78 versus <1.78	0.690	0.201 to 2.369	0.556
PLR	≥130 versus <130	0.785	0.222 to 2.767	0.707
LDH (IU/L)	≥ UNL versus < UNL	3.930	0.860 to 17.954	0.077
HBsAg status	Positive versus negative	1.849	0.442 to 7.729	0.400
Stage-modified IPI score	1-3 versus 0	11.582	1.716 to 78.189	**0.012**
Treatment regimens				
Breast Surgery	Present versus absent	0.759	0.186 to 3.098	0.701
Intrathecal injection	Present versus absent	2.410	0.626 to 9.277	0.201
Rituximab exposure	Present versus absent	1.094	0.243 to 4.914	0.906
Radiation therapy	Present versus absent	5.784	1.231 to 27.178	**0.026**
Refractory disease	Present versus absent	2.994	0.611 to 14.673	0.176

Note: BMI, body mass index; CNS, central nervous system; HBsAg, hepatitis B surface antigen; GCB, germinal center B-cell like. LDH, lactate dehydrogenase. CI, confidence intervals; NLR, neutrophil-lymphocyte Ratio; IPI, international prognostic index; PLR, platelet-lymphocyte ratio; UNL. Upper Normal Limit; WBC, white blood cell; HR, hazard ratio.

robust predictive index for CNS relapse in patients with primary breast DLBCL, supported by a significant bootstrap 95% CI (1.745–40846613) (Table 3). Additionally, we presented the cumulative incidence of CNS relapse based on the stage-modified IPI score (Fig. 1). Patients with a score of 0 experienced no CNS relapses at the 2- and 5-year marks, with only a single case (2.7%, 1/37) emerging after 10 years. Conversely, patients scoring 1 or higher exhibited a cumulative incidence of CNS relapse of 7.7% (3/39) at 2 years, which rose to 15.4% (6/39) at 5 years, and further increased to 23.1% (9/39) at the 10-year evaluation.

4. Discussion

The prognosis of primary breast DLBCL has shown significant improvement; however, the high incidence of CNS spread remains a clinical challenge in DLBCL treatment [5]. The ongoing discussion revolves around whether there is indeed a higher rate of CNS relapse in primary breast DLBCL [2]. However, our observations, as well as those of other researchers [3] suggest a sustained risk of CNS progression or relapse that persists beyond a long-term horizon (more than 5 years) from the time of diagnosis. In the era of immunochemotherapy, the proposed CNS-IPI incorporates individual IPI factors, in addition to kidney and/or adrenal gland involvement, establishing a three-risk group model for CNS relapse in DLBCL patients [9]. In our study, we noted a 2-year rate of CNS relapse of approximately 3.9% among primary breast DLBCL patients, categorizing them within the intermediate-risk category [9]. However, when evaluated using the CNS-IPI, all primary breast DLBCL patients with CNS involvement were categorized as low-risk (Supplemental Table 1). Consequently, the CNS-IPI model exhibits limited utility in predicting CNS recurrence in primary breast DLBCL.

In our present study, utilizing the CRR model, we have identified the stage-modified IPI score as a significant risk factor for CNS relapse in patients with primary breast DLBCL. The stage-modified IPI considers four indicators: age, disease stage (specifically, stage IIE), LDH levels, and ECOG performance status [3,15]. Notably, recent experimental evidence suggests that aged brains express c-c motif chemokine ligand 19 (CCL19), which promotes the retention of lymphoma cells, contributing to the formation of CNS lymphomas [22]. This supports the observation that old age is linked to a higher incidence of CNS relapse in DLBCL [3,8]. Our findings align with those reported by Hosein et al. [3], who observed a higher incidence of CNS relapse among primary breast DLBCL patients with stage IIE disease, elevated LDH, or a high stage-modified IPI (2–4), when comparing patients with and without CNS relapse. Schmitz et al.'s study [9] further supports our observations. In their multivariable analysis of the validation cohort, LDH levels and the

Table 3
Multivariate analysis of association between Stage-modified IPI score and the time to CNS relapse.

	Multivariate analysis			
Adjusted variables	HR	95% CI	P value	Bootstrap 95%CI
Stage-modified IPI score	**12.945**	**1.606–104.375**	**0.016**	**1.745–40846613**
Radiation therapy	7.258	1.534–34.344	0.012	/
Rituximab exposure	1.269	0.268–6.003	0.764	/
Intrathecal injection	1.511	0.401–5.688	0.542	/
Breast Surgery	0.88	0.234–3.307	0.85	/
HBsAg status	1.494	0.640–3.487	0.354	/

Note: CI, confidence intervals; CNS, central nervous system; IPI, international prognostic index; HBsAg, hepatitis B surface antigen; HR, hazard ratio.

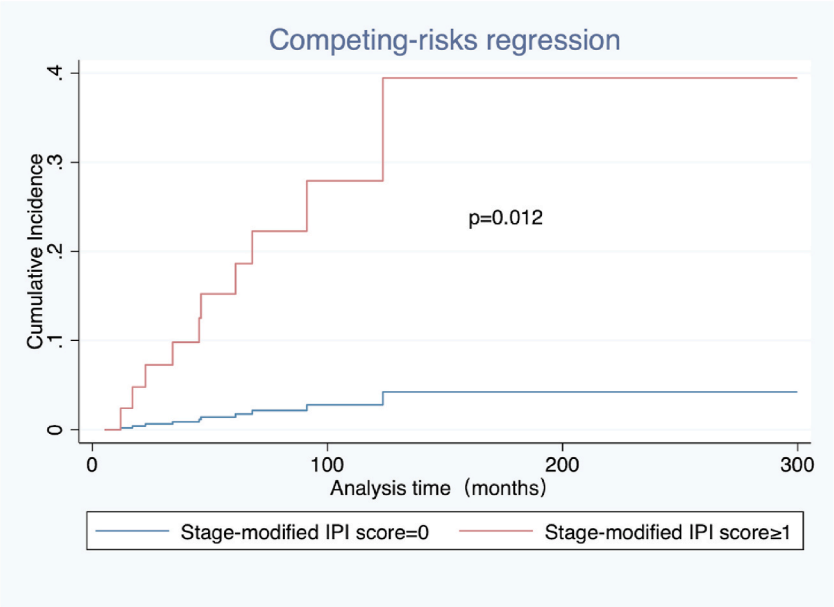

Fig. 1. Cumulative incidence of central nervous system relapse by stage-modified IPI score. Competing risk curve was generated using the Fine and Gray method, and p-values for the comparison of cumulative incidence curves were calculated using Gray's test. IPI, international prognostic index.

involvement of more than one extranodal site were identified as factors associated with CNS relapse. However, it is crucial to emphasize the necessity for validation of the stage-modified IPI through a prospective clinical trial to confirm its predictive value and clinical applicability.

In recent years, researchers have suggested that molecular support rather than anatomic location may cause the risk of CNS invasion [23,24]. It is noted that a higher prevalence of MCD subtype (based on co-occurrence of $MYD88^{L265P}$ and CD79B mutations) [23] in the secondary DLBCL of the CNS than observed in a reference cohort of relapsed DLBCL without CNS involvement [23,24]. Indeed, primary breast DLBCL with frequent co-occurrence of $MYD88^{L265P}$ and CD79B mutations has a spectrum of aggressive lymphoma [25–28]. However, we were unable to assess the link of the MCD subtype or high-grade B-cell lymphoma (double-hit) phenotype to the risk of CNS relapse in primary breast DLBCL [29] in this retrospective study. Our findings do not suggest a clear association between the cell-of-origin for non-GCB [24] subtypes and CNS recurrence. It's worth noting that the absence of this association may be, in part, due to the evaluation of misclassification using immunohistochemistry rather than gene-expression profiling [30]. Additionally, it's important to acknowledge that a substantial proportion of primary breast DLBCL cases are likely to fall within the non-GCB subtype, potentially reducing their utility in predicting CNS relapse. Despite classifying half of the patients with primary breast DLBCL into the CNS high-risk group based on the stage-modified IPI score, only a small proportion (22.6%–25.0%) of patients eventually experienced a CNS relapse (Table 1). Additionally, we identified radiation therapy as a risk factor for CNS relapse in primary breast DLBCL. Patients who underwent radiation therapy exhibited a higher frequency of refractory disease and a lower likelihood of rituximab exposure, as shown in Supplementary Table 2. These patients were found to be associated with a poorer prognosis in DLBCL. Moreover, Hu et al. found no correlation between CD5-positivity and CNS involvement in primary breast DLBCL [4]. Therefore, integrating molecular and genetic predictors of CNS relapse into primary breast DLBCL could improve the prediction model. In the future, further genetic and molecular data must be analyzed in the context of a high risk of primary breast DLBCL relapse in the CNS.

Treatment recommendations for primary breast DLBCL are not well established [2]. Considering the high-risk nature of CNS relapse subgroups from a clinical perspective, there is a compelling case for implementing additional aggressive CNS-directed prophylaxis [29]. However, optimal strategies for reducing CNS relapse still warrant further investigation [11]. Like other studies [11], prophylactic intrathecal injections have not significantly reduced CNS relapse in our cohort. While the effectiveness of CNS prophylaxis continues to be a topic of debate, patients with a high CNS-IPI score but no evidence of CNS involvement, as indicated by modern screening technologies, remain strong candidates for CNS prophylaxis. Innovative therapies may present rational options for prophylactic use [11]. The high-risk CNS relapse group may benefit from a combination of aggressive first-line therapy, intrathecal methotrexate, and systemic administration of multiple drugs capable of crossing the blood-brain barrier. For instance, drugs such as ibrutinib, lenalidomide, and immune checkpoint inhibitors have demonstrated potential efficacy against CNS DLBCL [31–35], and recent research has shown their compatibility with immunochemotherapy [36–38]. Indeed, both ibrutinib and lenalidomide are fundamentally effective for non-GCB type DLBCL [39] and represent promising prophylactic methods, given that the majority of primary breast DLBCL cases are non-GCB type DLBCL. Based on these rationale arguments, we intend to assess the impact of these drugs on preventing CNS relapse in a high-risk population of primary breast DLBCL patients.

The limitations of this study include the inherent nature of retrospective studies, the small sample size, and the absence of validation with external datasets. A large multicenter prospective clinical study with a corresponding translational program should be

carried out in the future.

5. Conclusions

In summary, patients with primary breast DLBCL who have a high stage-modified IPI score may experience a worse clinical outcome and a relatively higher risk of CNS failure. To enhance the precision of the prediction model, further investigations into the genetic and molecular factors associated with CNS relapse are warranted.

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Patient and public involvement

Patients and/or the public were not involved in this research's design, conduct, reporting, or dissemination plans.

Patient consent for publication

Not applicable.

Ethics approval

This study was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center (ZRB1612167-18).

Data availability statements

This article's underlying data cannot be shared publicly for ethical/privacy reasons.

CRediT authorship contribution statement

Guang-Liang Chen: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pin Guo:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis. **Jin Wang:** Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Data curation. **Bao-Hua Yu:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Xiaonan Hong:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Junning Cao:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Fangfang Lv:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Data curation.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to enhance the grammatical accuracy. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26795.

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