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Original Article

Clinical Characteristics and Prognostic Factors in Primary Breast Diffuse Large B-Cell Lymphoma

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Abstract. ***Background*: Primary breast diffuse large B-cell lymphoma (PB-DLBCL) is a rare subtype of non-Hodgkin lymphoma (NHL) with limited data on the clinical features and prognostic factors.**
Patients and Methods: **A consecutive cohort of patients with PB-DLBCL was retrospectively analyzed in our hospital from February 1997 through July 2018. The primary endpoint is overall survival (OS) contributing to any cause.**
Results: **A total of 76 patients were diagnosed with PB-DLBCL. The median age at diagnosis was 51 years (range: 25-80 years), with female prevalence (98.7%). Forty (52.6%) patients had right-sided breast involvement but no bilateral breast involvement at diagnosis. Overall, disease stages IE and IIE were seen in 55 (72.4%) and 21 (27.6%) patients, respectively. According to the stage-modified International Prognostic Index (IPI), 37 (48.7%) patients were classified in the very good risk group (IPI 0). Of the 72 patients available, the non-germinal center B-cell (non-GCB) subtype of DLBCL was observed in 66 (91.6%) patients. All patients received anthracycline-based chemotherapy, 56 (73.7%) with rituximab, 31 (40.8%) also with additional radiation therapy, and 14 (18.4%) patients received a prophylactic intrathecal injection. Seven (9.2%) patients had refractory disease. With a median follow-up of 6.8 years (range 0.4-25.0 years), 10 (13.2%) patients had a relapse in the central nervous system (CNS) site. The 5-year and 10-year OS of all the patients was 97.2% (95% CI: 99.3-89.5) and 84.8% (95% CI: 70.0-93.5), respectively. The median OS was not reached. The median progression-free survival (PFS) was 10.3 years for patients with PB-DLBCL. The 5-year PFS of all the patients was 76.3% (95% CI: 64.6-84.6). Univariate analysis revealed several prognostic factors, including stage-modified IPI, breast surgery, refractory disease, and CNS relapse. Multivariate analyses produced two independent prognostic factors for patients with PB-DLBCL, including stage-modified IPI score (2-3 versus 0) (hazard ratio: 19.114, 95% CI 1.841 to 198.451, p=0.013) and CNS relapse (hazard ratio: 5.522, 95% CI 1.059 to 28.788, p=0.043).**
Conclusion: **In our cohort, PB-DLBCL clinical features are similar to prior literature reports. Stage-modified IPI score and CNS relapse were associated with overall survival.**

Keywords: Breast; Diffuse large B-cell lymphoma; Prognostic factors; Relapse; Central nervous system.

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Introduction. Primary breast diffuse large B-cell lymphoma (PB-DLBCL) is an aggressive non-Hodgkin lymphoma (NHL) that affects the breast with or without regional lymph node involvement.[1,2,3,4] PB-DLBCL is primarily presented as a painless unilateral breast mass in women,[3,4,5] often misdiagnosed with breast carcinoma.[6] The increase in pathological data revealed a predominance of a non-germinal center B-cell (non-GCB) phenotype in PB-DLBCL.[3,7,8,9,10,11,12] However, most studies included a small sample for analysis, and the optimal treatment approach is not yet clear. Indeed, a rapid rise in the incidence of PB-DLBCL has been identified.[13,14] Additionally, younger or breast cancer patients with hormone therapy have an increased risk of developing NHL.[15]

To date, significant advances have been made in the genetic subtypes of DLBCL with different prognoses,[16,17] as well as in the molecular features of PB-DLBCL.[18,19,20] The revolution of the therapeutic strategies of PB-DLBCL with new emerging targeted therapies requires more knowledge of PB-DLBCL.[19,20,21] Furthermore, the incidence rate of central nervous system (CNS) relapse is higher in primary breast DLBCL than those in nodal DLBCL,[2,22] despite the widespread use of prophylactic intrathecal injection.[23] Nevertheless, the Asian population of PB-DLBCL was analyzed in limited research and a lack of a long-term follow-up.[24,25,26,27,28] Consequently, further understanding of the clinical features and prognostic factors of PB-DLBCL remains of interest.

We, therefore, conducted this retrospective study to investigate the clinical features, treatment outcomes, and prognosis in patients with PB-DLBCL. The primary endpoint of this study was the overall survival (OS).

Patients and Methods

Participants and Study design. We retrospectively reviewed data from the department of cancer prevention at Fudan University Shanghai Cancer Center (FUSCC) of patients who received a diagnosis of PB-DLBCL[29] between February 1997 and July 2018 (**Figure 1**). This study was approved by the Institutional Review Board of the FUSCC (ZRB1612167-18). Eligibility criteria required a confirmed pathological diagnosis of DLBCL according to the 2017 WHO classification of lymphoid neoplasms and localized disease (involvement of breast and localized lymph nodes). Patients with transformed DLBCL from low-grade lymphoma or other types of lymphoma and patients with incomplete data after diagnosis were excluded. Electronic medical records were used to obtain demographic and clinical variables, laboratory values, and medications. The primary outcome of interest was OS, measured as the time from the diagnosis of PB-DLBCL to death attributed to any cause; the last follow-up date was October 01, 2021. Progression-free survival (PFS) was calculated as the time from the date of diagnosis to disease progression or death from any cause. Mortality data and the timing of death were obtained from the department of cancer prevention, FUSCC. Five patients (6.6%) were considered lost to follow-up if the last visit was >12 months before the end of the study.

The stage-modified International Prognostic Index (IPI) score was assessed as previously described.[2,22,30] The GCB and non-GCB subtypes of DLBCL were determined using all the available information by Hans criteria.[31] Response assessment was carried out as in previous reports, according to the International Working Group response criteria.[2,32] Relapse refers to lymphoma, which recurs or develops after a period of complete remission. When the lymphoma does not or only partially responds to first-line chemotherapy is called refractory. Body Mass Index (BMI) is measured by a person's weight in kilograms divided by the square of height in meters.

Statistical analysis. All statistical analyses were two-sided and conducted with the IBM SPSS Statistics 26.0 or GraphPad Prism software 9.0. The association between demographic, clinical, or laboratory variables and the primary outcome (OS) were assessed using univariate Kaplan-Meier (KM) analysis (a stratified log-rank test) and multivariate Cox regression models as previously reported.[33] Briefly, the prognostic effect of each factor was analyzed by a log-rank test. Clinically relevant covariates (p<0.15) identified in univariate analyses were included in multivariate models. In addition, Cox's proportional hazards (Cox's PH) were assessed, and time-varying Cox regression analysis (Forward: LR) (entry significance level=0.05, exit significance level=0.1) was used to evaluate independent factors for survival. A two-sided P-value < 0.05 was considered statistically significant.

Results. Between February 1997 and July 2018, a consecutive cohort of 76 patients with PB-DLBCL was included in this study (**Figure 1**). The clinical-related characteristics and univariate analysis of patients with PB-DLBCL are shown in **Table 1**. The median age at diagnosis was 51 years (range: 25-80), and 98.7% of the patients were female. At presentation, only one (1.3%) patient presented with B-symptoms or poor performance status (Eastern Cooperative Oncology Group (ECOG) ≥2). Forty (52.6%) patients had a right breast lesion at diagnosis. No bilateral breast involvement at diagnosis was observed. Among all patients, 55 (72.4%) had disease stage IE, and 21 (27.6%) had IIE. The stage-modified IPI was 0 or 1 in 68 patients (89.5%). Of the 72 patients with available immunohistochemistry, the subtypes of DLBCL were non-GCB in 66 (91.6%) patients. Nine (11.8%) patients were positive for hepatitis B surface antigen upon diagnosis.

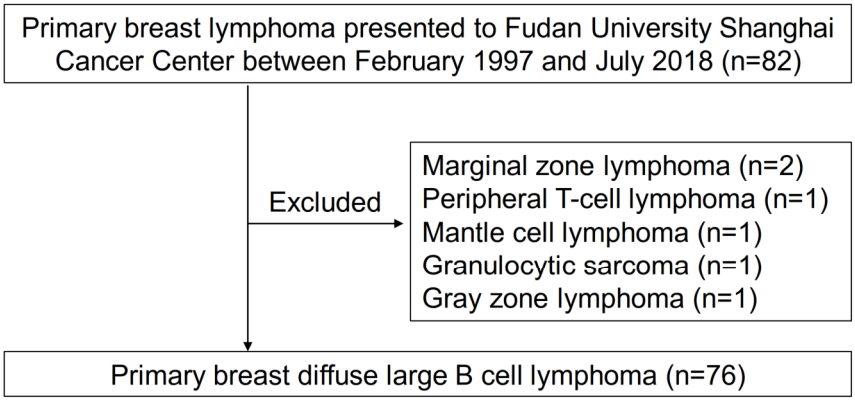

Figure 1. Algorithm of the study cohort selection of primary breast diffuse large B-cell lymphoma.

Table 1. Characteristics and univariate analysis of patients with primary breast diffuse large B-cell lymphoma.

Characteristic	Overall (N = 76)		Univariate analysis	
	No. of patients	%	Hazard Ratio	*p*-value
Age > 60 years	20	26.3	3.673	0.152
Female	75	98.7	22.273	0.546
BMI ≥25#	25	32.9	1.176	0.814
Laterality of tumor in right	40	52.6	0.618	0.508
Stage IIE	21	27.6	4.322	0.057
IPI score ≥ 2	3	3.9	0.048	0.782
Stage-modified IPI score				**0.000**
0	37	48.7	-	
1	31	40.8	2.743	
2-3	8	10.5	34.709	
Tumor size (≥ 50 mm in diameter) (68 cases)	14	20.6	1.445	0.493
Lactate dehydrogenase ≥ 250 IU/L	6	7.9	1.830	0.572
HBsAg positive	9	11.8	3.735	0.094
HBcAb positive	37	48.7	1.295	0.713
Non-GCB (72 cases)	66	91.6	0.435	0.420
Breast Surgery*	53	69.7	**0.161**	**0.006**
Prophylactic intrathecal injection	14	18.4	0.887	0.911
Rituximab exposure	56	73.7	0.851	0.848
Radiation therapy	31	40.8	3.424	0.110
Relapse disease	21	27.6	1.261	0.750
Refractory disease	7	9.2	**4.981**	**0.033**
CNS relapse	10	13.2	**9.412**	**0.000**

Note: HR, hazard ratio; CI, confidence intervals; BMI, body mass index; CNS, central nervous system; CTX, chemotherapy; R-CHOP, R-rituximab, C-cyclophosphamide, H-doxorubicin hydrochloride, O-vincristine, P-prednisone; IPI, international prognostic index; HBsAg, Hepatitis B surface antigen; HBcAb, hepatitis B core antibody; GCB, Germinal center B-cell like. *Four patients received a breast modified radical mastectomy surgery. # Two patients with obesity.

In our cohort, all patients were treated with anthracycline-based chemotherapy following the diagnosis of PB-DLBCL; 14 (18.4%) patients received a prophylactic intrathecal injection for CNS relapse (**Table 1**). Fifty-three (69.7%) patients had breast surgery prior to frontline chemotherapy. Fifty-six (73.7%) patients were treated with chemotherapy plus rituximab regimens. Radiation therapy (RT) after the frontline chemotherapy was administered in 31 (40.8%) patients. After a median follow-up of 6.8 years (range 0.4-25.0 years), eight (10.5%) patients died. The median OS was not reached (**Figure 2A**). The 5-year and 10-year OS of all the patients was 97.2% (95% CI: 99.3-89.5) and 84.8% (95% CI: 70.0-93.5), respectively. The median PFS was 10.3 years for patients with PB-DLBCL (**Figure 2B**). The 5-year PFS of all the patients was 76.3% (95% CI: 64.6-84.6). At the end of the frontline chemotherapy, five (6.6%) patients achieved a partial response (PR), and two (2.6%) progressed during treatment. A total of 28 (36.8%) patients had a relapse or refractory disease, with 7 (9.2%) classified as a refractory disease. CNS relapse occurred in 10 (13.2%) patients. The median time from the initial diagnosis to CNS relapse was 3.8 years (range: 1.0-10.3 years), and survival after CNS relapse in patients with PB-DLBCL was 34.4 months.

In univariate analysis (**Table1**), prognostic factors that retained statistical significance for OS were stage-modified IPI score (p=0.000) (**Figure 3A**), breast surgery (p=0.006) (**Figure 3B**), refractory disease (p=0.033) (**Figure 3C**), and CNS relapse (p=0.000) (**Figure 3D**). However, the two factors that have independent prognostic significance in multivariate analysis are stage-modified IPI score and CNS relapse (**Table 2**).

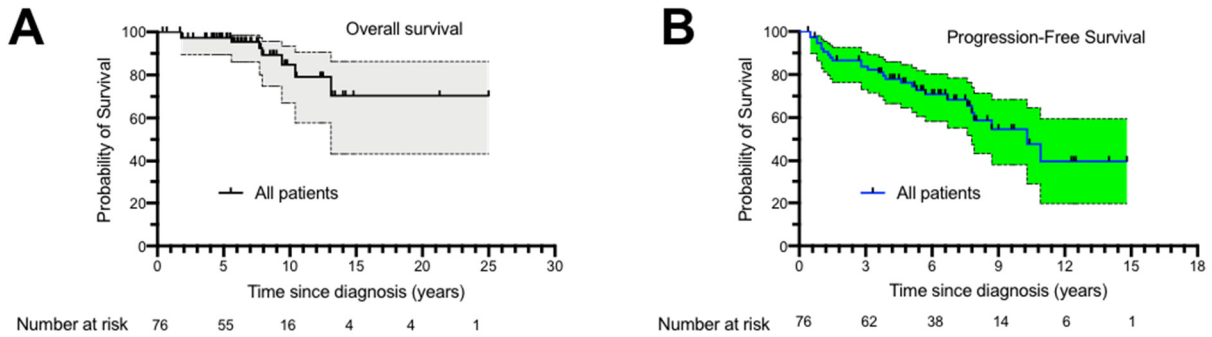

Figure 2. Overall survival (**A**) and progression-free survival (**B**) for patients with primary breast diffuse large B-cell lymphoma (N = 76).

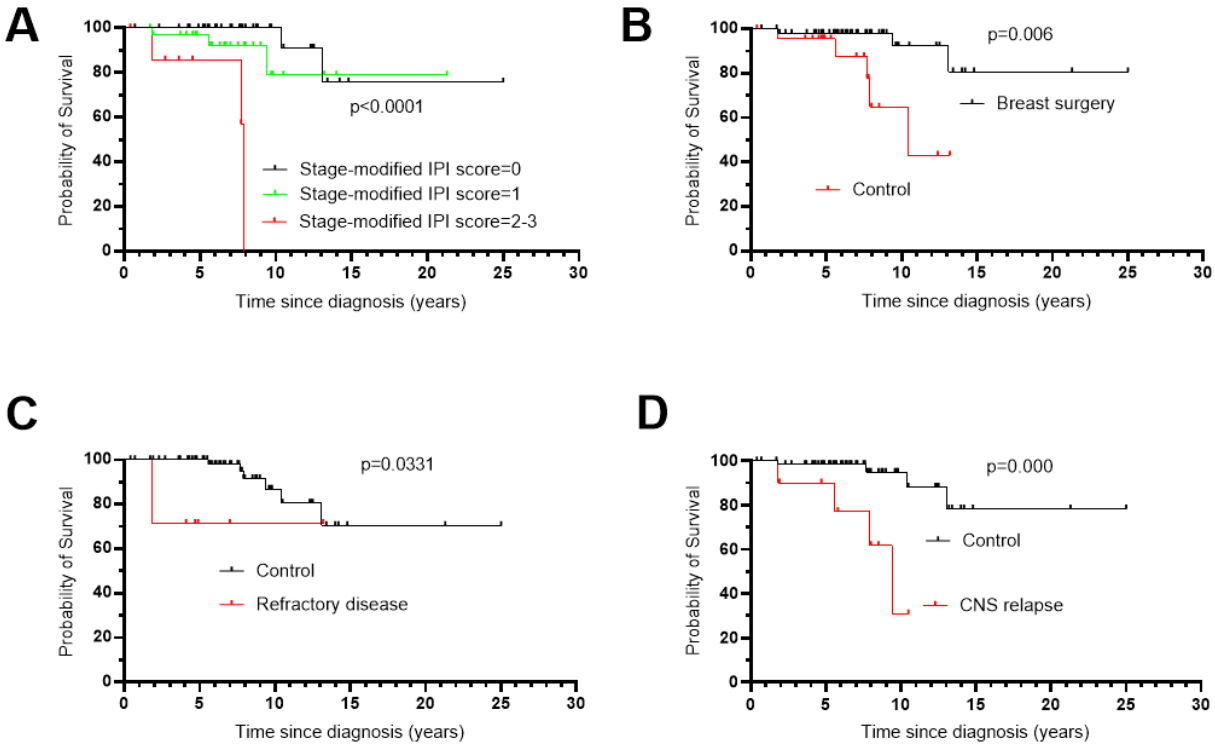

Figure 3. The Kaplan–Meier curves showing the impact of prognostic factors on overall survival. Analysis of overall survival of patients with primary breast diffuse large B-cell lymphoma were stratified based on stage-modified IPI (**A**); breast surgery (**B**); refractory disease (**C**); and CNS relapse (**D**).

Table 2. Multivariable Cox regression analysis (p<0.1).

Factors	Hazard Ratio	95% CI	p-value
CNS relapse	5.522	1.059 to 28.788	**0.043**
Stage-modified IPI score			**0.033**
0	reference		
1	2.283	0.348 to 14.966	0.39
2-3	19.114	1.841 to 198.451	**0.013**

Note: CI, confidence intervals; CNS, central nervous system; HBsAg, Hepatitis B surface antigen; IPI, international prognostic index. Adjusted covariates include Age (> 60 years), log (Time) * Age, Breast surgery, Stage II, Radiation therapy, CNS relapse, Refractory disease, Stage-modified IPI score, HBsAg positive.

Discussion. According to the current literature in this study, the PB-DLBC was the most frequent histologic subtype of primary breast lymphoma, a well-defined subtype of non-Hodgkin lymphoma (NHL);[1,2,11,13,22,34,35] the initial clinical presentation of PB-DLBCL was consistent with the published literature.[2,6,34,36] Most patients with PB-DLBCL were female aged less than 60 years, were unilaterally breast lumpy, and slightly more frequent on the right side. In addition, our data confirmed that the stage-modified IPI score is a major independent prognostic factor for PB-DLBCL.[2,6,30,36] Furthermore, a high rate of CNS relapse in our cohort was observed over a long follow-up and was found to be another important independent prognostic factor for OS. For considerable patients who have already received immunochemotherapy, RT, and prophylactic intrathecal injection,[23] other approaches to reducing CNS relapse still require exploration.

In the present study, the 10-year OS of the PB-DLBCL patients was 84.8% (95% CI: 70.0-93.5). The superior outcome is probably due to early screening, diagnosis, and multiple management approaches.[37] In our cohort, less than one-fourth of patients have a tumor diameter of more than 50 mm, which may preclude the adverse effect of bulky disease on the clinical outcome of PB-DLBCL.[38] Nearly half of our PB-DLBCL cohort was a younger population, which may partially explain the good prognosis. In addition, increased BMI does not seem to impact on survival of PB-DLBCL. Indeed, the risk and death of DLBCL patients are largely affected by chronic infection,[39,40,41,42,43,44] including hepatitis B virus infection.[45,46,47] However, our data found that HBsAg-positive status is not associated with OS (p=0.094). In the era of precision medicine, HBsAg-positive influence on OS in patients with PB-DLBCL should be evaluated in prospective studies.

The optimal therapeutic strategies for PB-DLBCL remain largely unrevealed. No benefit from breast mastectomy seems to have reached a consensus in patients with primary breast lymphoma.[5,6,34,48] In the present study, breast surgery, which consists primarily of lumpectomy (**Table 1**), is associated with an improved OS in univariate analysis but lost in the multivariate analysis (**Table 2**). Indeed, a study based on Surveillance, Epidemiology, and End Results (SEER) database analysis supports our findings.[37] In our opinion, breast surgery can provide perfect local control and sufficient samples for a precise diagnosis of disease.[35] However, a prospective investigation needs to establish whether the prognosis of PB-DLBCL can benefit from a rapid and accurate diagnosis and molecular identification.

In contrast to previous reports,[49,50] RT is not associated with improved OS (p=0.110). One possible explanation is the unfavorable characteristics of PB-DLBCL patients receiving an additional RT in our cohort. However, this raised a concern about the late complications of RT on PB-DLBCL, as the tumor-involved field of PB-DLBCL included several key organs of the heart and lungs. Therefore, the precise selection of PB-DLBCL patients for additional RT may be the subject of further research. Furthermore, in our study, rituximab use was not associated with a survival benefit,[2] although there is some controversial data.[51]

To date, a non-GCB phenotype of PB-DLBCL is associated with a poor prognosis.[52,53,54,55] However, the non-GCB phenotype of PB-DLBCL was not associated with the OS in the KM analysis of our cohort. An elevated incidence of CNS relapse was identified as an independent unfavorable OS factor. It could be associated with the intrinsic biological characteristics of the non-GC phenotype,[22] mutation of myeloid differentiation 88 (MYD88), and a cluster of differentiation 79b (CD79b).[18,19,56,57,58] However, due to the limited data available, our cohort did not analyze the role of the genomic mutation of MYD88 and CD79b in the prognosis of the OS. Indeed, the activated B cell-like (ABC) subtype of DLBCL with B cell receptor (BCR) and MYD88 mutations potentially respond to

Bruton's tyrosine kinase (BTK) inhibitor.[21,59] In the future, the impact of the BTK inhibitor on the incidence of CNS relapse and the prognosis in PB-DLBCL need to be assessed.

The small sample size and the inherent nature of observational and retrospective studies limited the current research. Therefore, we adjusted some known prognostic factors on DLBCL. Still, did not examine the role of Chinese traditional medicine, Epstein-Barr virus (EBV) infection, oncogenic gene mutation, or other confounding factors associated with treatment and DLBCL. Furthermore, assessment of CNS involvement

was not carried out in all patients at diagnosis. However, PB-DLBCL as a rare disease is far from being fully recognized. Therefore, the clinical features identified and several independent prognostic factors can help improve daily practice and guide the design of future clinical trials in this disease.

In summary, stage-modified IPI score and CNS relapse are valuable predictors for the prognosis of PB-DLBCL. However, additional efforts are required to decrease the rate of CNS relapse.

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