Clinical Features and Outcomes of Primary Breast Diffuse Large B-Cell Lymphoma: A Matched-Pair Study

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ABSTRACT

BACKGROUND: The influence of the breast as the primary site on the outcome of diffuse large B-cell lymphoma (DLBCL) and further changes in therapeutic strategies remain unclear. We aimed to compare the outcomes between primary breast and non-breast DLBCL and analyze the genetic profiles of some of the study cohorts using next-generation sequencing.

METHODS: This matched-pair study reviewed the medical records of 19 patients with stage I and II primary breast DLBCL diagnosed between January 2005 and December 2021 on the basis of the Wiseman and Liao criteria, and we used 1:4 propensity score matching to identify patients with non-breast DLBCL as the control group. The overall response rate, progression-free survival (PFS), and overall survival (OS) were the outcome measures.

RESULTS: Patients with primary breast and non-breast DLBCL had a 5-year PFS of 72.6% and 86.9%, respectively ($P = .206$). These 2 groups also had comparable 5-year OS (86.9% vs 87.8%; $P = .772$). The breast as the primary site was not associated with inferior PFS (hazard ratio [HR]: 2.14; 95% CI: 0.66-6.96; $P = .206$) and OS (HR: 1.26; 95% CI: 0.27-5.93; $P = .772$).

CONCLUSION: Patients with primary breast DLBCL and those with non-breast DLBCL had comparable PFS and OS under rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or R-CHOP-like regimens. Further investigations of the mutation profile, its clinical impact, potential central nervous system relapse, and prognosis of primary breast DLBCL are required.

KEYWORDS: DLBCL, breast, NGS, PFS, OS

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of non-Hodgkin lymphoma (NHL), accounting for 30% to 40% of newly diagnosed patients with NHL.[1] Most patients with DLBCL respond to standard treatment with the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). However, 30% of DLBCL cases are refractory to this treatment.[2]

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Although the revised International Prognostic Index (R-IPI) score and Lugano classification significantly predict the outcome of DLBCL,[3,4] the primary site of DLBCL may also be a prognostic factor. For example, primary central nervous system (CNS) DLBCL has worse outcomes than other types of DLBCL.[5] In contrast, patients with primary mediastinal B-cell lymphoma have excellent outcomes, showing a 5-year overall survival (OS) of 97%.[6] However, the influence of the breast as the primary site on the outcome of DLBCL and further changes in the therapeutic strategies remain unclear.

The primary breast lymphoma accounts for only 0.5% of breast malignancies and 2% of NHLs.[7] According to Wiseman and Liao's criteria, primary breast lymphoma is defined as having only ipsilateral axillary lymph node involvement without a previous history of NHL and multiple-site involvement.[8] Nonetheless, the World Health Organization (WHO) 2016 revised classification and the 5th edition (beta version) of the WHO classification of lymphoma do not specifically designate primary breast lymphoma as a distinct category.[9,10] Among the various pathological subtypes of NHL, non-germinal center DLBCL is the dominant subtype of primary breast lymphoma.[11]

The treatment protocols for primary breast lymphoma have changed over the past decades. While surgical intervention was the therapeutic option for primary breast lymphoma,[7] studies of primary breast DLBCL conducted by the International Extranodal Lymphoma Study Group (IELSG) and the Rare Cancer Network demonstrated inferior survival with mastectomy.[12,13] Radiotherapy may be an alternative treatment approach. Although radiotherapy can improve local control and progression-free survival (PFS) of primary breast lymphoma, the OS benefit is inconclusive.[12,13] Anthracycline-based chemotherapeutic regimens with rituximab remain the standard of care for primary breast DLBCL.[14] Because of the controversy regarding the higher incidence of CNS involvement and relapse rate of primary breast lymphoma,[15] the potential benefits of prophylactic intrathecal chemotherapy are uncertain.[16]

Primary breast lymphoma has previously shown an inferior prognosis in comparison with non-breast lymphoma.[17] However, the US surveillance, epidemiology, and end results program (SEER) registry found that stage I and II primary breast DLBCL and non-breast DLBCL had comparable OS.[18] This investigation aimed to compare the clinical features and treatment outcomes between primary breast and non-breast DLBCL. In addition, we analyzed genetic profiles using next-generation sequencing (NGS) in some study cases.

Methods

Patients

Medical records of 19 patients with stage I and II primary breast DLBCL diagnosed between January 2005 and December 2021 at the Taichung Veterans General Hospital and China Medical University Hospital were retrospectively reviewed. The median follow-up time was 4.85 years (range: 0.5-16.4 years). We used criteria proposed by Wiseman and Liao[8] to confirm the diagnosis of primary breast DLBCL. To further analyze the various outcomes, we used propensity scores, including sex, age, and Ann Arbor stage, in a 1:4 ratio to match primary breast DLBCL with non-breast DLBCL as the control group. Age was matched at 10-year intervals. When numbers of patients for the matching control group were insufficient, we first matched the Ann Arbor stage and classified the

matched patients in the near-age group as control cases. Patients with primary CNS DLBCL and those who did not complete the treatment were excluded from the non-breast DLBCL group. Ultimately, the control group included 76 patients. This study was approved by the Institutional Review Boards of China Medical University Hospital (CMUH111-REC2-028) and Taichung Veterans General Hospital (CE21513A). Owing to the retrospective nature of the study, the institutional review board waived the requirement for informed patient consent.

Definitions and outcome measurements

We used the response evaluation criteria in lymphoma 2017 criteria to evaluate treatment responses.[19] Revised International Prognostic Index and CNS-IPI scores of each patient were reviewed,[3,20] and Han's criteria was used to determine cell of origin. A double expressor was defined when MYC ($\geqslant$40%) and BCL-2 ($\geqslant$50%) were both positive.[21] Progression-free survival was calculated from the date of diagnosis until progression, mortality, or last follow-up. Overall survival was calculated from the date of diagnosis and censored by death.

Gene profile analysis

We used NGS to analyze 2 samples of primary breast DLBCL and 5 samples of non-breast DLBCL. Briefly, we used the QIAamp DNA Formalin-fixed Paraffin-Embedded Tissue Kit (Qiagen, Hilden, Germany) to extract genomic DNA from formalin-fixed paraffin-embedded specimens. The library construction was established using a Human Comprehensive Cancer Panel (Qiagen, GeneGlobe ID CDHS-3501Z, Catalog No. 333515, Hilden, Germany), which covers 275 oncogenes. The prepared library was then loaded onto an Illumina sequencing system (Nextseq550/NovaSeq6000, San Diego, CA, USA) for subsequent experiments. We stored the FastQ files from the targeted DNA libraries in the CLC Genomics Workbench 20 (QIAGEN, Demark) for read trimming, alignment, and variant calling. To identify high-confidence (pathogenic) variant calls, we followed the ACMG/AMP guidelines and the QIAGEN somatic workflow within the QIAGEN Clinical Insight Translational & Interpret software. Variant pathogenicity was assessed by identifying variants with a minimum coverage of 500 reads and allele frequency >5%. Pathogenic or likely pathogenic variants were confirmed using the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) (Supplemental File for variant calling).

Statistical analysis

We used Fisher exact tests or chi-square test to compare categorical variables between primary breast and non-breast DLBCL groups, as indicated. The Mann-Whitney U test was

used for comparisons of continuous variables. Both PFS and OS were investigated using the Kaplan-Meier method and stratified log-rank tests. This study used Cox proportional hazards regression to analyze prognostic factors for PFS and OS. The regression was quantified as hazard ratios (HRs) and their accompanying 95% CIs. All statistical analyses were performed using IBM SPSS version 22.0 for Windows (New York, NY, USA). $P < .05$ was considered statistically significant.

Results

Comparison of patients' characteristics

The median ages of the primary breast DLBCL and non-breast DLBCL groups were 52 and 54 years, respectively ($P = .798$). Patients in these 2 groups had comparable stage distribution ($P = 1.000$), R-IPI ($P = .304$), CNS-IPI ($P = .288$), cell of origin ($P = .431$), and double expression ($P = .646$) (Table 1). Regarding extranodal involvement within the control group of 78 cases, 40 patients (51.3%) exhibited extranodal lesions. Among these cases, the most prevalent site of involvement was the stomach (19 cases), followed by the intestine (7 cases) and the nasal cavity and paranasal sinuses (3 cases).

Treatments and treatment response

Regarding treatment, 94.7% (18/19) of patients in the primary breast DLBCL group and 93.4% (71/76) of patients in the non-breast DLBCL groups received CHOP or CHOP-like regimens ($P = 1.000$). In the primary breast DLBCL cohort, 2 patients (10.5%) received fewer than 6 cycles of chemotherapy, while in the non-breast DLBCL group, 12 patients (15.8%) received fewer than 6 cycles of chemotherapy ($P = .728$). In addition, 6 cases in the primary breast DLBCL group (31.6%) underwent radiotherapy and 3 (15.8%) received surgical intervention. In the non-breast DLBCL group, 22.4% (17/76) of patients received radiotherapy and 18.4% (14/76) underwent surgical treatment. Notably, these surgical interventions were primarily conducted to alleviate symptoms or facilitate diagnosis, rather than to achieve curative outcomes.

In treatment response, the complete response (CR) rates in the primary breast DLBCL and non-breast DLBCL groups were 100% and 93.4%, respectively. The treatment response was not substantially different between these 2 groups of patients ($P = .663$) (Table 2).

Furthermore, relapse and progression rates in the primary breast DLBCL group and non-breast DLBCL group were 21.1% (4/19) and 14.4% (11/79), respectively ($P = .328$). Regarding relapse sites, all relapses in patients with primary breast DLBCL occurred over non-primary sites. In the non-breast DLBCL group, 72.7% (8/11) of relapses involved non-primary sites. Central nervous system relapse was observed in 10.5% (2/19) and 2.6% (2/76) of the patients in the primary breast DLBCL group and non-breast DLBCL group, respectively ($P = .177$). These results suggested that these 2 groups of patients had similar relapse patterns (Table 3).

Survival comparison

The 5-year PFS rates of primary breast and non-breast DLBCL patients were 72.6% and 86.9%, respectively ($P = .206$) (Figure 1A). Besides, the 5-year OS rates were 86.9% and 87.8%, respectively ($P = .772$) in these 2 groups (Figure 1B). Further details of the survival comparisons are shown in Supplemental Table 1.

We further identified the prognostic factors for both PFS and OS using Cox proportional hazards regression. Age, performance status of *Eastern Cooperative Oncology Group* (ECOG), Ann Arbor stage, lactate dehydrogenase (LDH), R-IPI score, primary breast DLBCL or non-breast DLBCL, cycles of chemotherapy, and treatment modalities were the independent variables. Univariate analyses revealed that age ≥ 60 years (HR: 7.68; 95% CI: 2.56-23.04; $P < 0.001$), ECOG performance status ≥ 2 (HR: 4.54; 95% CI: 1.25-16.50; $P = .022$), and higher R-IPI scores (HR: 7.21; 95% CI: 1.61-32.21; $P = .010$) were related to poor PFS. However, only age ≥ 60 years (HR: 3.96; 95% CI, 1.02-15.37; $P = .047$) remained significant in multivariate analyses. For OS, univariate analyses demonstrated that age ≥ 60 years (HR: 7.62; 95% CI: 2.19-26.53; $P = .001$), ECOG performance status ≥ 2 (HR: 8.03; 95% CI: 2.02-31.97; $P = .003$), LDH level above normal range (HR: 3.50; 95% CI: 1.02-11.97; $P = .046$), and inferior R-IPI (HR: 5.22; 95% CI: 1.13-24.18; $P = .035$) were potential factors for an inferior OS. However, in the multivariate analyses, only individuals aged ≥ 60 years exhibited a significant effect (HR: 8.94; 95% CI: 1.31-60.86; $P = .025$). Notably, primary breast DLBCL was not an independent factor for inferior PFS or OS in our study (Table 4).

Genetic analysis by NGS

We used NGS to analyze the genetic profiles of 2 primary breast DLBCL samples and 5 non-breast DLBCL samples. Clinicopathological characteristics of these 7 patients are presented in Supplemental Table 2. Briefly, both primary breast DLBCL cases and 3 of the 5 non-breast DLBCL cases were of the ABC type. Mutations in *BCR*, *CHEK2*, *NF1*, and *KMT2C* were common in both groups. One primary breast DLBCL specimen and 2 non-breast DLBCL specimens had *CD79B* and *MYD88* mutations. In addition, *PRDM1*, *ARID1A*, *KMT2D*, and *EZH2* mutations were found in primary breast DLBCL cases, which was consistent with the genetic profile of DLBCL reported in previous studies.[22,23] The genetic profiles of these 2 groups did not substantially differ (Figure 2).

Discussion

This matched-pair study showed that primary breast DLBCL and non-breast DLBCL patients had comparable PFS and OS. Furthermore, Cox regression analysis demonstrated that the breast as the primary site was not a significant factor for inferior PFS or OS. Moreover, the genetic profiles did not differ between the primary breast and non-breast DLBCL groups in the limited number of samples analyzed in this study.

Table 1. Comparison of patient characteristics between primary breast DLBCL and non-breast DLBCL groups.

	PRIMARY BREAST DLBCL GROUP (N = 19)		NON-BREAST DLBCL GROUP (N = 76)		*P*-VALUE
Age, median, y (range)	52	(31-80)	54	(30-84)	.798[a]
Age at diagnosis ≥ 60 years	3	(15.8%)	17	(22.4%)	.755[b]
Ann Arbor stage, n (%)					1.000[c]
IE	9	(47.4%)	36	(47.4%)	
IIE	10	(52.6%)	40	(52.6%)	
ECOG performance, n (%)					.344[b]
<2	19	(100%)	70	(92.1%)	
≥2	0	(0%)	6	(7.9%)	
LDH level, n (%)					.161[c]
Within normal range	15	(78.9%)	47	(61.8%)	
Above normal range	4	(21.1%)	29	(38.2%)	
B symptoms, n (%)					.755[b]
No	16	(84.2%)	59	(77.6%)	
Yes	3	(15.8%)	17	(22.4%)	
R-IPI score, n (%)					.304[c]
Very good (0)	12	(63.2%)	38	(50.0%)	
Good (1–2)/Poor (3–5)	7	(36.8%)	38	(50.0%)	
CNS IPI score, n (%)					.288[b]
Low (0–1)	18	(94.7%)	63	(82.9%)	
Intermediate (2–3)	1	(5.3%)	13	(17.1%)	
Cell of origin, n (%)					.431[c]
Non-GCB	8	(42.1%)	27	(35.5%)	
GCB	6	(31.6%)	17	(22.4%)	
Unknown	5	(26.3%)	32	(42.1%)	
Double expressor, n (%)					.646[c]
Non-double expressor	3	(15.8%)	15	(19.7%)	
Double expressor	6	(31.6%)	16	(21.1%)	
Unknown	10	(52.6%)	45	(59.2%)	

Abbreviations: CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell; LDH, lactate dehydrogenase; R-IPI, Revised International Prognostic Index.
[a]Mann-Whitney test.
[b]Fisher exact test.
[c]Chi-square test.

The outcome impact of primary breast sites in DLBCL remains controversial. The IELSG study revealed an estimated 54% of 5-year PFS and 63% of 5-year OS among 204 primary breast lymphoma cases from 1980 to 2003.[13] Besides, the 5-year PFS and OS of patients with primary breast lymphoma in the Rare Cancer Network study were 49% and 53%, respectively,[12] which were comparable to the results of the IELSG study. Notably, the outcomes of primary breast lymphoma appear to improve over time. Data from the US SEER registry revealed that the 5-year relative survival of primary breast lymphoma was 45.9% in 1975-1984 and 90% in 2005-18, 2012.[24] Using a matched-pair analysis, Yhim et al[25] confirmed this result, demonstrating that the 3-year OS rates (82.2 vs 90.7%, *P* = .345) and 3-year PFS rates (70.0% vs 82.2%, *P* = .154) did

Table 2. Treatment and treatment response comparison between primary breast DLBCL and non-breast DLBCL groups.

	PRIMARY BREAST DLBCL GROUP (N = 19)		NON-BREAST DLBCL GROUP (N = 76)		*P*-VALUE
Chemotherapy, n (%)					1.000
CVP-like	1	(5.3%)	5	(6.6%)	
CHOP-like	18	(94.7%)	71	(93.4%)	
Cycles of chemotherapy					.728
<6 cycles	2	(10.5%)	12	(15.8%)	
≥6 cycles	17	(89.5%)	64	(84.2%)	
Rituximab, n (%)	19	(100%)	76	(100%)	—
Radiotherapy, n (%)	6	(31.6%)	17	(22.4%)	.388
Operation, n (%)	3	(15.8%)	14	(18.4%)	1.000
Treatment response, n (%)					.663
Complete response	19	(100%)	71	(93.4%)	
Partial response	0	(0%)	4	(5.3%)	
Progressive disease	0	(0%)	1	(1.3%)	

Abbreviation: DLBCL, diffuse large B-cell lymphoma CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone.
Fisher exact test.

Table 3. Comparison of relapse pattern between primary breast DLBCL and non-breast DLBCL groups.

	PRIMARY BREAST DLBCL GROUP (N = 19)		NON-BREAST DLBCL GROUP (N = 76)		*P*-VALUE
Relapsed pattern, n (%)					.328
No relapse	15	(78.9%)	65	(85.5%)	
Non-primary site relapse	4	(21.1%)	8	(10.5%)	
Primary site relapse	0	(0%)	3	(3.9%)	
CNS relapse, n (%)					.177
No CNS relapse	17	(89.5%)	74	(97.4%)	
CNS relapse	2	(10.5%)	2	(2.6%)	

Abbreviations: CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma.
Fisher exact test.

not substantially differ between primary breast DLBCL and stage I/II nodal DLBCL. Our findings are consistent with previously reported data (Supplemental Table 3). Importantly, the Cox regression analysis in the current study validated the result that the breast as the primary site did not relate to worse PFS and OS.

The potential explanations for the improved outcomes of primary breast DLBCL over time are conceivably related to the incorporation of rituximab as a standard chemoimmuno-therapeutic agent. Hu et al[26] demonstrated that rituximab treatment significantly reduced the risk of disease recurrence and progression in primary breast DLBCL. Notably, our study cohort received rituximab treatment. The CR rate of primary breast DLBCL group can be as high as 100%. Genetic

mutations may partially explain the improved outcomes with rituximab therapy in primary breast DLBCL. Previous studies have shown that rituximab effectively overcomes PRDM1-associated resistance to chemotherapy.[27,28] Next-generation sequencing analysis in the current study identified the PRDM1 mutation in one of the 2 patients with primary breast DLBCL. However, not all studies have supported the clinical benefits of rituximab treatment for primary breast DLBCL. Zhang et al[29] found that patients with primary breast DLBCL treated with or without rituximab had similar 5-year PFS (90% vs 71.4%; *P* = .285) and 5-year OS (90% vs 71.4%; *P* = .239). A retrospective study by Aviles et al[11] also validated this result, showing that patients of primary breast DLBCL had comparable 5-year PFS (64% vs 69%; *P* = .66) and 5-year OS (53% vs 52%; *P* = .50)
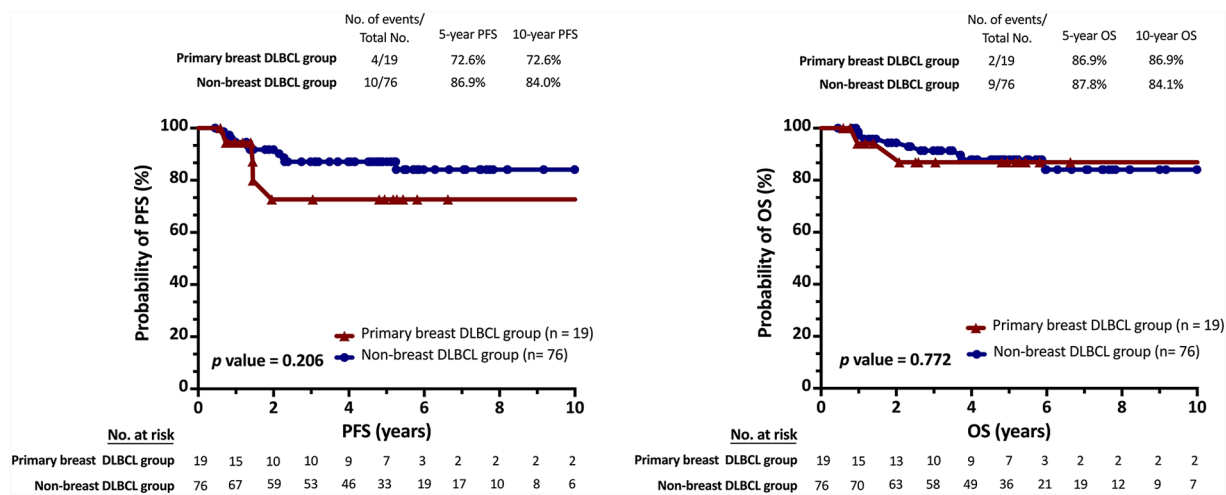
Figure 1. Comparison of survival data. (A) The 5-year progression-free survival (PFS) rates in the primary breast diffuse large B-cell lymphoma (DLBCL) and non-breast DLBCL groups were 72.6% and 86.9%, respectively (*P* = .206). (B) The 5-year overall survival (OS) rate in these 2 groups was 86.9% and 87.8%, respectively (*P* = .772).

after R-CHOP and CHOP treatments. Taken together, these data suggest that the influence of rituximab on the prognosis of primary breast DLBCL requires more investigation.

Our study demonstrated that primary breast DLBCL and non-breast DLBCL had similar genetic profiles, as analyzed via NGS. *MYD88* and *CD79B* mutations are frequently found in breast lymphomas.[30,31] Furthermore, *PIM1*, *CRAD11*, and *PRDM1* were reported mutations in breast DLBCL.[23,28,32] Our results revealed *PRDM1*, *MYD88*, and *CD79B* mutations in one primary breast DLBCL case. Although both *MYD88* and *CD79B* mutations suggest worse prognosis in DLBCL,[22,33] the current analysis did not yield similar results because of the limited number of analyzed specimens. Notably, 2 cases of primary breast DLBCL in our study cohort carried the NF1 mutation, which is associated with a favorable risk in DLBCL.[34] This could be further evidence for the satisfactory prognosis of primary breast DLBCL in the current study. Next-generation sequencing analysis also revealed *BCR*, *CHEK2*, *KMT2C*, and *CYLD* mutations in the primary breast DLBCL samples. However, their impact on the prognosis of primary breast DLBCL remains unclear.

Lymphoma with breast involvement increases the risk of CNS recurrence.[35] The CNS recurrence rate in primary breast lymphoma varies from 5% to 16%.[12,13,15] Two of the 19 (10.5%) patients with primary breast DLBCL experienced CNS relapse in our study cohort. This result is comparable to the data from previous studies. Owing to a limited number of patients, the CNS relapse rate was not substantially different between the primary breast DLBCL and non-breast DLBCL groups in our study (10.5% vs 2.6%; *P* = .177). The application of prophylactic intrathecal chemotherapy to reduce CNS relapse in breast DLBCL patients remains debatable.[36] Although 2 cases of primary breast DLBCL in the current study underwent prophylactic intrathecal chemotherapy, and both were free from CNS relapse, no consolidative evidence supports routine CNS

prophylaxis in this clinical scenario. Notably, prophylactic intrathecal chemotherapy did not always decrease the CNS relapse rate. In a phase II study, 33 breast lymphoma patients received R-CHOP and intrathecal CNS prophylaxis with MTX. However, the 2-year CNS relapse rate remained as high as 12.5%.[16] Whether intrathecal chemotherapy can effectively prevent CNS relapse in primary breast DLBCL remains unclear and warrants further investigation.

The strength of this study was the direct comparison between primary breast DLBCL and DLBCL of other origins, with data matched for sex, age, and Ann Arbor stage. A retrospective matched-pair study design with a small study cohort was the major limitation of our study. Owing to the restricted number of patients included in the analysis, this study solely employed propensity score matching based on age, sex, and Ann Arbor stage. Furthermore, most lacked data pertaining to MYC, BCL2, and BCL6, leading to incomplete information for the double-hit classification. Furthermore, statuses of bulky disease and comorbidities were not recorded. In addition, NGS studies were performed in only a few cases because we could not obtain specimens, which made the genetic profiles inconclusive. Further studies with more comprehensive analyses of the genetic mutation profile of patients with primary breast DLBCL and its clinical impact are urgently needed.

Conclusion
This study matched sex, Ann Arbor stage, and age, comparing primary breast DLBCL to DLBCL of other origins. The treatment responses of these 2 groups were satisfactory and showed no significant differences. Moreover, patients with primary breast DLBCL and non-breast DLBCL had comparable PFS and OS. With a more extensive study cohort, further investigation of the mutation profile, its clinical impact, potential CNS relapse, and prognosis of primary breast DLBCL is required.

Table 4. Risk factors for PFS and OS by Cox regression.

	PFS		OS	
	UNIVARIATE	MULTIVARIATE	UNIVARIATE	MULTIVARIATE
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
DLBCL				
Non-breast DLBCL group	1.00	1.00	1.00	1.00
Primary breast DLBCL group	1.54 (0.48-4.98)	2.23 (0.64-7.70)	1.16 (0.25-5.38)	2.97 (0.52-16.81)
Age at diagnosis				
<60 years	1.00	1.00	1.00	1.00
≥60 years	7.68 (2.56-23.04)	3.96 (1.02-15.37)	7.62 (2.19-26.53)	8.94 (1.31-60.86)
Ann Arbor stage				
IE	1.00		1.00	
IIE	1.26 (0.45-3.54)		1.57 (0.46-5.39)	
ECOG performance				
<2	1.00	1.00	1.00	1.00
≥2	4.54 (1.25-16.50)	1.77 (0.43-7.23)	8.03 (2.02-31.97)	2.24 (0.46-11.02)
LDH level				
Within normal range	1.00		1.00	1.00
Above normal range	2.64 (0.91-7.61)		3.50 (1.02-11.97)	3.71 (0.77-17.75)
R-IPI score				
Very good (0)	1.00	1.00	1.00	1.00
Good (1-2)/Poor (3-5)	7.21 (1.61-32.21)	3.09 (0.52-18.57)	5.22 (1.13-24.18)	0.68 (0.07-6.93)
Treatment				
Chemotherapy only	1.00		1.00	
Chemotherapy with local therapy	2.19 (0.78-6.17)		0.77 (0.22-2.63)	
Chemotherapy cycles				
<6 cycles	1.00		1.00	
≥6 cycles	0.51 (0.14-1.83)		0.70 (0.15-3.26)	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-IPI, Revised International Prognostic Index.
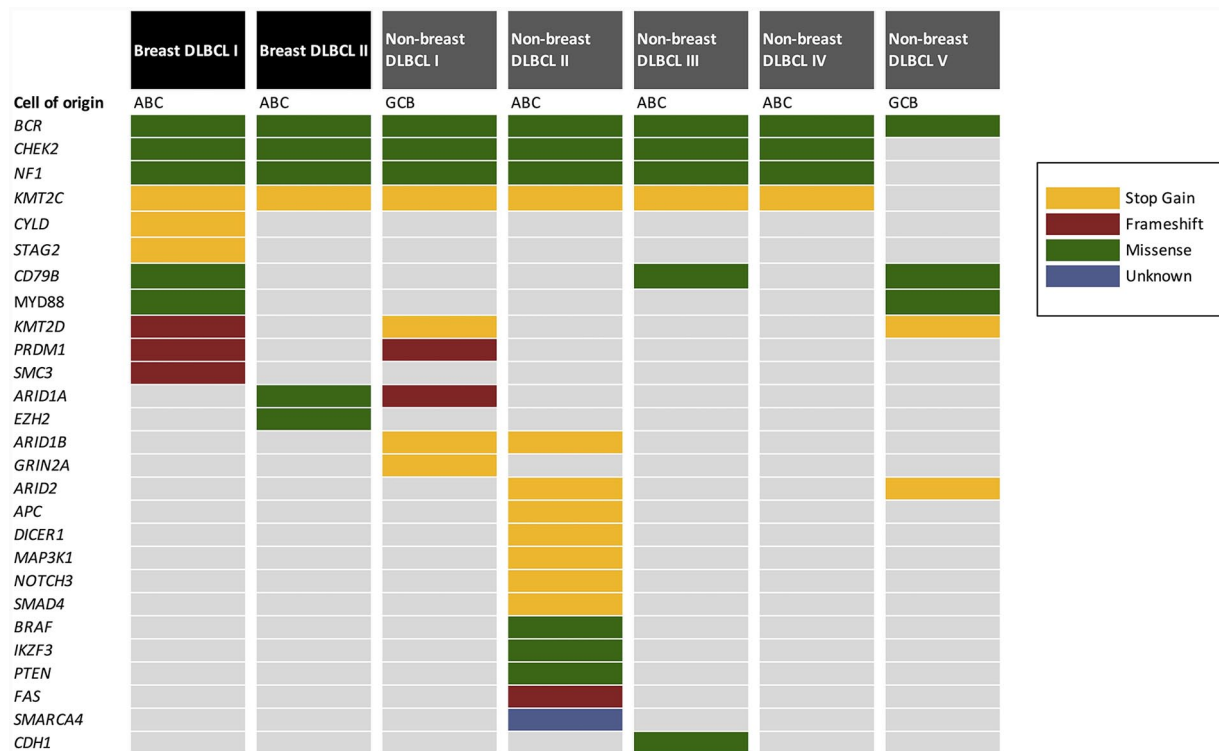
Figure 2. Genetic profile comparison between primary breast diffuse large B-cell lymphoma (DLBCL) and non-breast DLBCL. The *BCR, CHEK2, NF1,* and *KMT2C* mutations were common in both groups. One primary breast DLBCL and 2 non-breast DLBCL specimens showed *CD79B* and *MYD88* mutations. In addition, *PRDM1, ARID1A, KMT2D,* and *EZH2* were also detected in the primary breast DLBCL cases. The genetic profiles of these 2 groups were not significantly different.

Compliance With Ethical Standards

This study was approved by the Institutional Review Boards of China Medical University Hospital (CMUH111-REC2-028) and Taichung Veterans General Hospital (CE21513A). Due to the retrospective nature of the study, the institutional review board waived the requirement for obtaining informed patient consent.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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