Original article

Epidemiological features of primary breast lymphoma patients and development of a nomogram to predict survival

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Abstract

Background: Studies on the epidemiology and prognosis of primary breast lymphoma (PBL) are lack for low incidence. Therefore, we aimed to investigate the epidemiological characteristics of PBL and develop nomograms to predict patient survival.

Methods: Data of patients who were diagnosed with PBL from 1975 to 2011 and incidence rate of PBL from 1975 to 2017 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Time-varying multivariable Cox regression analysis was performed to identify independent prognostic factors for overall survival (OS) and disease-specific survival (DSS). Nomograms were constructed based on the independent prognostic factors identified in multivariate Cox regression analysis.

Results: A total of 1427 patients diagnosed with PBL were identified with the average age of 67.1 years. The overall incidence of PBL is 1.35/1,000,000 (adjusted to the United States standard population in 2000) from 1975 to 2017, with a significant upward trend by an annual percentage change (APC) of 2.91 (95% CI 2.29–3.94, P < 0.05). Age, sex, race, year of diagnosis, marital status, histological subtype, Ann Arbor Stage, and treatment modality were assessed as independent prognostic factors for OS and DSS by multivariable Cox regression (P < 0.05). Nomograms were constructed to predict the 1-, 3-, 5-, and 10-year OS and DSS. The concordance index (C-index) and calibration plots showed robustness and accuracy of the nomogram.

Conclusion: The overall incidence of PBL was steadily increasing over the past four decades. Nomograms constructed can predicting 1-, 3-, 5-, and 10-year OS and identify patients with high-risk PBL.

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1. Introduction

Primary breast lymphoma (PBL) is a rare malignancy accounting for only 0.5% of malignant breast neoplasms. It was first reported by Wiseman and Liao in 1972 and refers to the an extranodal lymphoma originating in the breast, with or without axillary lymph node metastasis [1]. A painless mass is the most common clinical manifestation of PBL. Other symptoms include local pain, inflammation, and lymphadenopathy. However, skin retraction, erythema, peau d’orange, and nipple changes are rarely present [2]. There are many histological subtypes of PBL, with diffuse large B-cell lymphoma (DLBCL) being the most common. Other histological types include Hodgkin lymphoma (HL), follicular lymphoma (FL), extranodal marginal zone lymphoma (MZL), mucosa-associated lymphoma (MALT), Burkitt lymphoma (BL), small B lymphocytic (SBL), lymphoplasmacytic lymphoma (LPL), mantle cell lymphoma...
(MCL), and T cell lymphoma (TCL), etc [3].

PBL is a rapidly progressing malignance with poor outcomes compared with other extranodal lymphoma [4]. The Ann Arbor clinical stage and International Prognostic Index (IPI) score are currently used to estimate the prognosis of PBL, although it is still difficult to assess prognosis accurately due to the variety of histological subtypes, the complexity of the influencing factors, as well as the low incidence [5–8]. The current understanding of PBL mainly comes from case reports or retrospective analysis of studies with small samples size. Detailed and specific information about the incidence, treatment, and survival of PBL in the large populations still needs to be addressed.

Thus, the present study was conducted based on data extracted from the Surveillance, Epidemiology, and End Results (SEER) database to present detailed and specific information about PBL. The epidemiological characteristics were compared between histological subtypes of PBL and the incidence, prognostic factors, and survival of PBL were detected. Prognostic nomograms were established to assist clinicians in accurately estimating the prognosis.

2. Materials and methods

2.1. Data source and patients enrollment

We extracted information on patients diagnosed with PBL from the SEER database. The SEER database currently includes patient data from 18 cancer registration centers, and collects comprehensive data about tumors for approximately 30% of the population in the United States of America [9]. The annual incidence rates for PBL were extracted from 1975 to 2017 to study national trends. All incidence rates for PBL were calculated.

To provide follow-up data for more than 5 years, individual patient data were extracted from 1975 to 2011. All data were extracted using SEER Stat software, version 8.3.6. Lymphoma classification was based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histological codes 9590–9599, 9650–9729, and primary sites limited to the breast were identified by site specific codes C50.0 to C50.9. To reduce bias caused by diagnosis and follow-up, we used the following inclusion and exclusion criteria. The inclusion criteria were: 1) microscopically confirmed diagnosis; 2) complete data; and 3) active follow-up. The exclusion criteria were: 1) data derived from autopsy or death certificate; or 2) incomplete data. Individual data relative to the following variables were extracted from the years 1975–2011: age, sex, race, year of diagnosis, marital status, laterality, histological subtype, Ann Arbor Stage, surgery, radiation, chemotherapy, survival months, vital status, and cause of death.

The outcomes of interest were overall survival (OS) and disease-specific survival (DSS). OS was defined as the time from the diagnosis of PBL to death attributed to any cause. DSS was defined as the time from the diagnosis of PBL to death attributed to PBL.

2.2. Statistical analyses

The incident rates, which were age-adjusted to the standard population of the United States in 2000, were calculated per 1,000,000 persons using SEER stat (version 8.3.6). Annual percentage changes (APCs) were calculated using SEER stat software. The 95% confidence intervals (CIs) and hazard ratios (HRs) were calculated.

Conventional Cox regression models were checked for the proportional hazards (PH) assumption, and time-varying Cox regression analysis was used to evaluate independent factors for survival and nomograms predicting 1-, 3-, 5- and 10-year OS and DSS were constructed based on the identified independent factors [10]. Harrell’s concordance index (C-index) was generated to assess the exact prognostic values of the nomogram. Calibration curves were constructed to verify whether the predicted survival and actual survival were in concordance. X-tile software was utilized to divide patients into the low-risk, medium-risk, and high-risk.

Statistical analysis was performed using R software (version 4.0.1) and x-tile (version 3.6.1). The R package included Table 1, survival, survminer, rms, and ggplot2. A two-sided P-value < 0.05 was considered statistically significant.

3. Result

3.1. Incidence of PBL

The overall incidence of PBL was 1.35/1,000,000 (adjusted to the US standard population in 2000) from 1975 to 2017, with a significant upward trend (APC = 2.91; 95% CI 2.29–3.94, P < 0.05). The incidence of three most frequent histological subtypes, namely, DLBCL, FL, and MALT, stably increased over time (Fig. 1 and Table 1). The incidence varied for different ethnicities. Among the black population, the incidence was 0.99/1,000,000 individuals, which was lower than that among white people (1.35/1,000,000). The incidence among American Indians, Alaskan natives, and Asian/Pacific Islanders was 1.39 per 1,000,000 individuals. The APC in whites from 1975 to 2017 was 2.96 (95% CI 2.24–3.28; P < 0.05). Across different age groups, the incidence of individuals aged over 60 years (5.877/1,000,000) was significantly higher than that of individuals aged under 60 years (0.45/1,000,000). Both age groups showed a statistically significant increase over time, with an APC of 2.54 (95% CI 1.44–3.65, P < 0.05) for patients aged under 60 years old and an APC of 2.93 (95% CI 2.19–3.67, P < 0.05) for patients aged 60 years or older. Considering sex, the incidence rate was 2.3/1,000,000 in females and 0.14/1,000,000 in males, and the APC for females was 3.66 (95% CI 3.05–4.27, P < 0.05).

3.2. Demographics of PBL patients

A total of 1427 patients with PBL were included in the study, and these were distributed into a training dataset or validation dataset randomly according to the ratio of 2:1. The characteristics of

| Table 1 | Incidence rate from 1975 to 2017. |
|---------|-------------------|
| Rate    | APC               |
| Overall | 1.35              | 2.91(2.29–3.94) |
| Age     |                   |
| <60     | 0.45              | 2.54(1.44–3.65) |
| ≥60     | 5.88              | 2.93(2.19–3.67) |
| Sex     |                   |
| Female  | 0.14              | 3.66(3.05–4.27) |
| Male    | 2.30              | NA               |
| Race    |                   |
| White   | 1.35              | 2.96(2.24–3.28) |
| Black   | 0.99              | NA               |
| others  | 1.39              | NA               |
| Laterality |               |
| Bilateral | 0.06             | NA               |
| Unilateral | 1.29            | 2.91(2.27–3.56) |
| Ann Arbor Stage |       |
| Stage I | 0.47              | NA               |
| Stage II| 0.19              | NA               |
| Stage III| 0.03             | NA               |
| Stage IV| 0.10              | NA               |
| Major subtype |          |
| DLBCL   | 0.56              | NA               |
| FL      | 0.20              | NA               |
| MALT    | 0.22              | NA               |
patients in the training and validation datasets were summarized in Table 2. The patients were aged 13–98 years, with an average age of 67.1 years. Based on the Ann Arbor Stage criteria, patients in stage 1 were the most, accounting for 60.8%. The proportions of patients in stage 2, stage 3, and stage 4 were 16.4%, 5.1%, and 17.7% respectively. Among various histopathological subtypes, DLBCL was the most common, followed by MALT and FL (Table 2).

The overall age at diagnosis was 67.1 years, but the age at diagnosis was lower in BL (56.1 years) and ALCT (54.1 years). FL had the highest 5-year OS rate (79.1%), but the 5-year OS rates of BL (46.2%), DLBCL (54.4%), and TCL (44.8%) were relatively lower (Table 3).

3.3. Survival analysis

The OS and DSS curves for the entire cohort of all patients were illustrated in Fig. 2. The median OS was 118 months and the OS rates at 1, 5, 10, and 15 years for all patients were 87.0%, 64.6%, 30.0%, and 9.4% respectively. Survival increased over time, and the survival rates of patients diagnosed in the years 1985–1993, 1994–2002, and 2003–2011 were all longer than for patients diagnosed from 1975 to 1984 ($P < 0.001$) (Fig. 3).

The Kaplan-Meier curves for the main subtypes are shown in Fig. 4. The median survival rate of patients with HL was the longest (312 months), and the median survival rates of those with FL, MALT, and SBL were relatively high (146, 155, and 156 months, respectively). The median survival rate of those with TCL (27 months) was the shortest. A more advanced Ann Arbor stage was significantly associated with worse OS and DSS. Patients with bilateral involvement had a shorter OS than patients with unilateral involvement ($P = 0.014$); however, there was no difference in terms of DSS between these two subgroups (Fig. 5).

Kaplan-Meier survival analysis was also performed stratifying patients according to age, sex, race, and marital status (Fig. 6). OS and DSS decreased with increasing age of patients. The prognoses of female patients and married patients were better than for other patient subgroups. Race had no effect on DSS or OS.

In terms of treatment strategies, patients who underwent the combination of surgery, radiotherapy and chemotherapy had better OS and DSS (Fig. 7).

3.4. Multivariable cox regression analysis and nomogram

Tests based on the PH assumption for conventional Cox regression are presented in Table 4. The test statistics suggest that all factors satisfied the PH assumption in both cox regression models at the 5% significance level except pathological typing, Ann Arbor stage and treatment strategy. The time-varying Cox regression analysis for OS and DSS showed that all variables were significant ($P < 0.05$) except for laterality (Table 5).

Excluding non-significant variables and those with modest significance, patient age, sex, race, marital status, histological classification, and Ann Arbor stage were used as factors to construct the nomogram for OS and DSS in the training dataset. The nomograms to predict OS and DSS at 1-, 3-, 5- and 10-year are shown in Fig. 8. Each variable corresponded to a specific point by drawing a straight line up to the points axis. The sum of the points could estimate the possibility of OS and DSS at 1-, 3-, 5- and 10-year.

The C-index was used to assess the discriminative ability of the nomogram. The C-index for the nomogram for the prediction of OS was 0.746 (95% CI 0.724–0.768) in the training dataset and 0.719 (95% CI 0.687–0.751) in the validation dataset, which indicated the
stability and effectiveness of the constructed nomogram. The discriminating superiority of the nomogram predicting DSS also performed well as reflected by C-index for both training dataset and validation dataset (0.764, 95% CI: 0.735–0.794, and 0.773, 95% CI: 0.732–0.813, respectively).

The calibration curves showed excellent consistency between the prediction and actual outcome for OS and DSS in both datasets. (Figs. 9 and 10).

### 3.5. Performance of the nomogram in stratifying risk

X-tile software was utilized to divide patients into the low-risk, medium-risk, and high-risk. The cutoff points were 71 and 101 (Fig. 11A and B). Moreover, 674, 302, 451 patients were categorized into the low-risk, medium-risk, and high-risk groups respectively. The high-risk patients (n = 451) significantly had the worst OS, and the low-risk patients (n = 674) had the best OS (P < 0.0001) based on the Kaplan-Meier analyses (Fig. 11C).

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**Table 2**

Baseline demographic and clinical characteristics of patients.

|                      | Overall (N = 1427) | Training Dataset (N = 951) | Validation Dataset (N = 476) |
|----------------------|--------------------|---------------------------|-------------------------------|
| **Year of diagnosis**|                    |                           |                               |
| 1975–1984            | 15 (1.1%)          | 10 (1.1%)                 | 5 (1.1%)                      |
| 1985–1993            | 121 (8.5%)         | 87 (9.1%)                 | 34 (7.1%)                     |
| 1994–2002            | 418 (29.3%)        | 264 (27.8%)               | 154 (32.4%)                   |
| 2003–2011            | 873 (61.2%)        | 590 (62.0%)               | 283 (59.5%)                   |
| **Age**              | Mean (SD)          |                           |                               |
| Mean (SD)            | 67.3 (14.8)        | 66.8 (15.0)               | 67.6 (14.4)                   |
| Median [Min, Max]    | 69.0 [130, 98.0]   | 69.0 [130, 98.0]          | 70.0 [200, 96.0]              |
| **Sex**              |                    |                           |                               |
| Female               | 1378 (96.6%)       | 916 (96.3%)               | 462 (97.1%)                   |
| Male                 | 49 (3.4%)          | 35 (3.7%)                 | 14 (2.9%)                     |
| **Race**             |                    |                           |                               |
| White                | 1195 (82.4%)       | 794 (83.5%)               | 401 (84.2%)                   |
| Black                | 104 (7.3%)         | 70 (7.4%)                 | 34 (7.1%)                     |
| Asian or Pacific Islander | 120 (8.4%)  | 82 (8.6%)                 | 38 (8.0%)                     |
| American Indian/Alaska Native | 8 (0.6%) | 5 (0.5%) | 3 (0.6%) |
| **Marital status**   |                    |                           |                               |
| Married              | 773 (54.2%)        | 526 (55.3%)               | 247 (51.9%)                   |
| Unmarried            | 478 (33.5%)        | 306 (32.2%)               | 172 (36.1%)                   |
| never married        | 176 (12.3%)        | 119 (12.5%)               | 57 (12.0%)                    |
| **Laterality**       |                    |                           |                               |
| Bilateral            | 64 (4.4%)          | 37 (3.9%)                 | 27 (5.7%)                     |
| Left                 | 615 (43.1%)        | 425 (44.7%)               | 190 (39.9%)                   |
| Right                | 748 (52.5%)        | 489 (51.4%)               | 259 (54.4%)                   |
| **Pathological type**|                    |                           |                               |
| DLBCL                | 645 (45.2%)        | 423 (44.5%)               | 222 (46.6%)                   |
| ALCL                 | 18 (1.3%)          | 11 (1.2%)                 | 7 (1.5%)                      |
| TCL                  | 29 (2.0%)          | 19 (2.0%)                 | 10 (2.1%)                     |
| HL                   | 14 (1.0%)          | 11 (1.2%)                 | 3 (0.6%)                      |
| MALT                 | 318 (22.3%)        | 217 (22.8%)               | 101 (21.2%)                   |
| BL                   | 26 (1.8%)          | 20 (2.1%)                 | 8 (1.6%)                      |
| FL                   | 278 (19.5%)        | 180 (18.9%)               | 98 (20.6%)                    |
| LPL                  | 18 (1.3%)          | 13 (1.4%)                 | 5 (1.1%)                      |
| SBL                  | 64 (4.5%)          | 44 (4.6%)                 | 20 (4.2%)                     |
| MCL                  | 17 (1.2%)          | 13 (1.4%)                 | 4 (0.8%)                      |
| **Ann Arbor Stage**  |                    |                           |                               |
| Stage I              | 867 (60.8%)        | 589 (61.9%)               | 278 (58.4%)                   |
| Stage II             | 234 (16.4%)        | 172 (18.1%)               | 62 (13.0%)                    |
| Stage III            | 73 (5.1%)          | 43 (4.5%)                 | 30 (6.3%)                     |
| Stage IV             | 253 (17.7%)        | 147 (15.5%)               | 106 (22.3%)                   |
| **Surgery**          |                    |                           |                               |
| No                   | 806 (56.5%)        | 528 (55.5%)               | 278 (58.4%)                   |
| Yes                  | 621 (43.5%)        | 423 (44.5%)               | 198 (41.6%)                   |
| **Radiation**        |                    |                           |                               |
| No/Unknown           | 909 (63.7%)        | 604 (63.5%)               | 305 (64.1%)                   |
| Yes                  | 518 (36.3%)        | 347 (36.5%)               | 171 (35.9%)                   |
| **Chemotherapy**     |                    |                           |                               |
| No/Unknown           | 677 (47.4%)        | 451 (47.4%)               | 226 (47.5%)                   |
| Yes                  | 750 (52.6%)        | 500 (52.6%)               | 250 (52.5%)                   |
| **Treatment modality**|                   |                           |                               |
| No treatment received| 213 (14.9%)        | 149 (15.6%)               | 64 (13.4%)                    |
| Surgery only         | 241 (16.9%)        | 165 (17.4%)               | 76 (16.0%)                    |
| Radiotherapy only    | 114 (8.0%)         | 80 (8.4%)                 | 34 (7.1%)                     |
| Chemotherapy only    | 304 (21.3%)        | 211 (22.2%)               | 93 (19.5%)                    |
| Radiotherapy + surgery| 109 (7.6%)     | 65 (6.8%)                 | 44 (9.2%)                     |
| Chemotherapy + surgery| 151 (10.6%)   | 90 (9.5%)                 | 61 (12.8%)                    |
| Chemotherapy + radiotherapy | 175 (12.3%) | 106 (11.1%) | 69 (14.5%) |
| Chemotherapy + radiotherapy + surgery | 120 (8.4%) | 85 (8.9%) | 35 (7.4%) |
4. Discussion

Few data are available on the incidence and survival of PBL for its low incidence, resulting in great difficulty in the assessment of prognosis and treatment. Using patient data registered in the SEER database, we calculated the incidence of PBL; evaluated clinical parameters, treatment outcomes, and prognostic factors; and also built nomograms for predicting the survival of patients with PBL.

Our study showed that the incidence rate of PBL was 1.35 per million people from 1975 to 2017 in United States of America. Incidence rate showed an increasing trend, with an APC of 2.91 (95% CI 2.29–3.94). Possible reasons for this increasing incidence of PBL are obscure but may be partly attributed to improved diagnosis and better registration systems, as well as lifestyle and environmental factors [11].

OS and DSS also showed an upward trend over time, which largely depends on the improvements in therapeutic strategies, especially the development of targeted treatments [12]. CD20 is highly expressed by all mature B-cells. The rapidly development of anti-CD20 monoclonal antibody has further improved the prognosis of CD20-positive B lymphoma in recent years [13,14].

Our study showed that the average age at diagnosis of PBL was 67.1 years, with a median age of 69 years, which is similar to the data reported in previous studies [15]. Advanced age was correlated...
Fig. 4. Survival analysis of PBL according to histological types: (A) OS; (B) DSS.
with worse outcome in terms of both OS and DSS. Elderly patients tended to have more comorbidities that could negatively affect the survival time directly as well as influence treatment doses for low tolerability [16,17]. Consistent with previous studies, the prevalence of PBL in males is much lower than that in females. Sex-based preferences were observed because estrogen plays an important role in the pathogenesis of PBL. Previous studies have shown that 29% of patients treated with estrogen replacement therapy had an increased risk of non-Hodgkin lymphoma (NHL) compared with women who had never undergone hormone treatment [18]. However, in our study, male patients tended to have worse DSS. This may be due to the lack of sufficient attention being paid to male patients, which may result in delayed diagnosis and incorrect treatment. In addition, race and marital status were significantly associated with survival. Asian or Pacific Islanders and married patients achieved more prolonged survival.

Among the evaluated clinicopathological variables, the Ann Arbor stage and histological subtypes were observed to be significantly associated with the survival of PBL patients. Ann Arbor stage was originally developed for HL and was revised at the Cotswolds Meeting in 1989; it is now widely used in clinical staging for both HL and NHL [19,20]. Our study showed that the Ann Arbor stage had a significant impact on OS and DSS. Patients with early-stage lymphoma tended to have better prognosis, consistent with previous studies [5,21–23]. Moreover, our result showed that different histological subtypes of PBL had distinct incidence and prognosis. The most common histopathological subtype of PBL in our study was DLBCL, accounting for 45.2%, followed by MALT (22.3%) and FL (19.5%), which is in line with a previous study [24]. Rarer histological types included ALCT, BL, SBL, LPL, TCL, MCL, and HL DLBCL is
Fig. 6. Overall survival of PBL according to (A) age, (C) sex, (E) race, and (G) marital status. Disease-specific survival of PBL according to (B) age, (D) sex, (F) race, and (H) marital status.
also associated with the highest recurrence rate [3]. But transformation maybe exist among various histology. Fruchart et al. reported that partial PBL cases are caused by histological changes from low-grade lymphoma by investigating the same specimen characterized as both MZL and DLCL concurrently. Niitsu et al. stated that partial DLBCL cases might lead to FL based on the evaluation of three patients with the germinal center B cell phenotype that carried 18q21/BCL2 translocations. More research on the incidence and transformation of PBL histological subtypes is needed. In our study, patients with HL had significantly better survival than those with NHL, as reported in most literature [25]. In our study, among NHL subtypes, MALT was significantly associated with the best OS, and TCL was associated with the worst OS, as also reported by previous studies, given its high invasiveness and poor response to treatment [26].

The treatment strategies for PBL varied broadly. Using alone or in combination of surgery, radiotherapy and chemotherapy was commonly. However, there is no standard guideline for PBL treatment up to date [8]. Chemotherapy was performed in more than half of the patients in our study, seemingly to be a more common therapy than surgery and radiation. The combination of surgery, radiotherapy, and chemotherapy had a significantly positive association with prolonged OS and DSS in our research.

Literature findings on the prognostic impacts of surgery in PBL patients are somewhat controversial. Uesato et al. indicated that enucleation of the tumor only, and not axillary dissection, could improve survival [27]. Nevertheless, an increasing number of studies showed that mastectomy could increase mortality [2,3,28]. However, as PBL is indistinguishable from breast carcinoma, surgery remains the initial treatment for most PBL patients. In conclusion, minimum surgery based on a histological diagnosis is indispensable, although surgical intervention other than biopsy is generally not recommended.

Chemo-immunotherapy and consolidation radiotherapy are widely used for the treatment of PBL [29]. Chemotherapy regimens that include anthracycline significantly improve OS and progression-free survival [3]. The addition of rituximab has markedly improved the survival of B-cell NHL [30–32]. The recommended treatment strategies based on previous studies included limited surgery, local radiation, and anthracycline-based chemotherapy, in which the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) is the most common chemotherapeutic approach [33,34]. In our study, the combination of surgery, radiation, and chemotherapy also can prolong OS and DSS significantly. But chemotherapy combined with radiotherapy is not significant. This may be partly attributed to the availability of incomplete data on treatment approaches in the SEER database, such as regimen, dose, and duration of chemotherapy and radiation therapy. But we also should reassess the role of surgery as most prior analysis has been conducted using retrospective studies based on small sample sizes, and there have been no randomized controlled trials for PBL. Thus, further investigation is needed for decision-making regarding the treatment of PBL.

Due to limited evidence on significant prognostic factors in PBL patients, prognostic prediction models for PBL patients are lacking. As an essential prediction model, the nomogram has currently become a widely used method for the individualized prediction of patient survival [35]. In this study, nomograms based on age, sex, race, marital status, Ann Arbor Stage, and histological type were built to predict 1-, 3-, 5-, and 10-year OS and DSS in PBL. The C-index and calibration curves were used to verify the predictive value of the nomogram. The obviously higher C-index indicated that the models estimate the discrimination well. The calibration curve showed consistency between the predicted and actual survival rates, ensuring the reliability of our prediction model.

Some limitations should be noted in this study. First, as this was a retrospective study, biases were unavoidable. Second, many variables that could have an impact on survival are not recorded in the SEER database, such as several biomarkers, B symptoms, and the IPI [36]. Therefore, many potential prognostic factors could not be included in the prediction model. Third, information regarding

| Variable                        | OS   | DSS  |
|---------------------------------|------|------|
| Years of diagnosis             | 0.405| 0.894|
| Age                            | 0.167| 0.158|
| Sex                            | 0.495| 0.289|
| Laterality                     | 0.548| 0.384|
| Classification                 | <0.001| <0.001|
| Ann Arbor Stage                | 0.002| 0.001|
| Marital status at diagnosis    | 0.196| 0.173|
| Race recode (W, B, AI, API)    | 0.648| 0.863|
| Treatment modality             | 0.011| 0.027|

| GLOBAL                         | <0.001| <0.001|
Despite these limitations, our study provides useful information on a reliable source for studying rare tumors in a large population. Nonetheless, the SEER database is still a limited resource due to the unbalance of ethnic distribution. More studies based on different regions and races are needed to balance the race distribution and make the results more generalized. Fourth, the patients included in our study may not be representative for the unbalance of ethnic distribution. Above all, caution should be exercised when interpreting the results. Treatment modality data is missing. Thus, it was difficult to accurately assess the effects of treatment. Above all, caution should be exercised when interpreting the results. Fourth, the patients included in our study may not be representative for the unbalance of ethnic distribution in the SEER database. More studies based on different regions and races are needed to balance the race distribution and make the results more generalized. Nonetheless, the SEER database is still a reliable source for studying rare tumors in a large population. Despite these limitations, our study provides useful information on the incidence, prognostic factors, and patient survival in PBL.

### 5. Conclusion

Our study shows that PBL is a rare type of lymphoma with an increasing trend in incidence in recent decades. Some factors associated with survival were identified, which provide new insights to improve the management of and healthcare for patients with PBL. Moreover, we also constructed a nomogram model of OS, which will assist clinicians in estimating prognosis accurately and establishing individualized treatment.
Fig. 8. Nomograms to predict Overall survival and Disease-specific survival for patients with PBL.

Fig. 9. Calibration curves of the nomogram for (A) 1-year, (B) 3-year, (C) 5-year, and (D) 10-year Overall survival.

Fig. 10. Calibration curves of the nomogram for (A) 1-year, (B) 3-year, (C) 5-year, and (D) 10-year Disease-specific survival.
Data availability statement

Publicly available datasets were analyzed in this study. This data can be found in the SEER database (https://seer.cancer.gov/).

Authors’ contributions

PF and LJ: conception of the work, data collection, data analysis, and drafting the article; MSD, CL, FJ, and QY: critical revision of the article; ALS and HY: conception of the work.

All authors read and approved the final manuscript and the corresponding author had final responsibility for the decision to submit for publication.

Availability of data and materials

Please contact the author for data requests.

Consent for publication

Not applicable.

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Ethics statement

This study was conducted in full compliance with the publication guidelines provided by SEER. The data were obtained from SEER, so the approval of an ethics committee was not needed.

Declaration of competing interest

The authors declare that they have no competing interests.

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