Epidemiological Features for Primary Lymphoma of the Female Genital Tract Patients and Development of a Nomogram to Predict Survival

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Research Article

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Abstract

Background: Primary lymphoma of the female genital tract (PLFGT) is a sporadic extranodal lymphoma. Its epidemiology and prognosis are not fully recognised. Our study aimed to construct and validate prognostic nomograms for predicting survival for patients with PLFGT.

Methods: Incidence rate from 1975 to 2017 and patients with PLFGT from 1975 to 2011 in the Surveillance, Epidemiology and End Results (SEER) database were retrospectively reviewed. The nomograms of OS and DSS were established according to the multivariate Cox regression analyses. The concordance index (C-index) and calibration plots were used to demonstrate its robustness and accuracy.

Results: A total of 617 PLFGT patients were identified. The overall incidence of PLFGT is 0.44/1,000,000 (adjusted to the US standard population in 2000) from 1975 to 2017. Age, histological subtype, Ann Arbor Stage, and therapeutic strategy were identified as independent prognostic factors for overall survival (OS) and disease-specific survival (DSS) by multivariate Cox regression ($P < 0.05$). Nomograms to predict 1-, 5-, and 10- year OS and DSS were established. The C-index and calibration plots showed a good discriminative ability and an optimal accuracy of the nomograms. Patients were devided into three risk groups according to the model of OS.

Conclusions: The nomograms were developed and validated as an individualized tool to predict OS and DSS.

Introduction

Non-Hodgkin's lymphoma (NHL) ranks seventh in terms of incidence among men and women, constituting 4% of new cancer cases and 3% of cancer-related fatalities annually[1]. Extranodal lymphoma accounts for approximately 25–40% of them[2]. But primary lymphoma of the female genital tract (PLFGT) is uncommon, accounting for 1.5% of extranodal NHL, mainly in the ovary[3–5].

The majority of PFGSL patients were middle-aged females, aged over 40 years[6, 7]. Its clinical manifestation is not specific as vaginal bleeding, pelvic mass, vaginal secretion, and abdominal pain[5]. It is easy to be confused with the other malignant tumor at the genital tract[6, 8]. Therefore, histological and immunophenotypic analyses for diagnosis are indispensable[9].

PFGSL has a good prognosis compared with other extranodal lymphoma. Ann Arbor stage was commonly applied to evaluate the outcome, and the international prognostic index (IPI) was developed to provide more accurate prediction of prognosis[10]. But there is no specified prognostic model of PFGSL for its low incidence, as most literature about PFGSL is single case reports.

Therefore, we conducted this research based on the Surveillance, Epidemiology, and End Results (SEER) database to explore epidemiological and clinical characteristics about PFGSL. Prognostic nomograms were established to assist clinicians in estimating the prognosis accurately.

Material And Methods

Data Source and Patients Enrollment

Information on patients with PFGSL was obtained from the SEER database by SEER Stat software, version 8.3.6, which contains cancer cases in 18 tumor registration centers and covers approximately 28% of the population in the United States. The annual incidence rate was extracted from 1975 to 2017 to study the trend of the incidence rate. All incidence rates are age-adjusted.

Patient data is extracted from 1975 to 2011 to follow-up at least five years. Lymphoma was identified by the International Classification of Diseases for Oncology Version 3 (ICD-O-3) histology codes 9590–9599, 9650–9729 and originated from the female genital tract was identified using the lesion number C50.1-C57.9.

Inclusion and exclusion criteria are established as followed to ensure the reliability of data. Inclusion criteria, 1) diagnosis by microscopically confirmed; 2) diagnosed between 1975 to 2011; 3) active follow-up. Exclusion criteria: 1) reporting from autopsy and date certificate; 2) unknown Ann Arbor stage.

Individual data derived from the SEER database included demographic data (age, race, year of diagnosis, marital status), tumor characteristics (primary site, histological subtype, Ann Arbor Stage), treatment strategy (surgery, radiation, chemotherapy)and survival information (survival months, vital status, cause of death).

Overall survival (OS) and disease-specific survival (DSS) are the endpoint of interest which are defined as the duration from the diagnosis of PFGSL to death or last follow-up due to any causes or PFGSL, respectively.

Statistical Analysis.

The incident rates (age-adjusted to the standard population of the United States in 2000) were calculated by SEER stat. The Kaplan-Meier curves for OS and CSS were drawn and analyzed by the log-rank test. The hazard ratio (HR) and the associated 95% confidence interval (CI) were calculated by multiple cox regression analysis to identify independent risk factors, used to construct the nomogram**s**. Internal and external validation were generated to measure the discrimination powers of the nomograms model using the concordance index (C-index) and calibration curve. Additionally, patients were categorized into three different risk groups based on the total nomogram score of OS.

All statistical analyses were performed using R software (version 4.0.1) and X-tile (version 3.6.1). The R package included Table1, survival, survminer, rms, and ggplot2. A two-sided P-value < 0.05 was considered statistically significant.

Table 1
Incidence rate from 1975 to 2017

	Rate (1,000,000)
Overall	0.44
Year of diagnosis	
1975–1985	0.2
1986–1996	0.4
1997–2007	0.59
2008–2017	0.39
Age	
< 40	0.15
40–59	0.59
≥ 60	1.01
Race	
White	0.41
Black	0.34
American Indians, Alaskan natives, and Asian/Pacific Islanders	0.44

Results

Incidence of PLFGT

The total incidence of PLFGT was 0.44/1,000,000 (adjusted to the US standard population in 2000) from 1975 to 2017. In the last 40 years, the incidence increased stably before 2005 and then decreased with incidence peaking from 1997 to 2007 (Figure 1). According to the race, the incidence of black (0.34/1,000,000) was lower than other people (0.41/1,000,000 for white, 0.44/1,000,000 for American Indians, Alaskan natives, and Asian/Pacific Islanders). Grouped by age, the incidence of patients upper 60 years was much higher than that of patients younger than 40 years and 40-59 years (Table 1).

Demographics of PBL patients

617 eligible patients with PLFGT are identified according to inclusion and exclusion criteria. Patients are allocated to training cohort or validation cohort randomly based on the ratio of 2:1. The demographic and clinicopathological features are compiled in Table 2.

In the whole study cohort, the median and the mean age at diagnosis were 55.0 and 55.3 years. More than half of the patients (52.8%) were diagnosed between 2003 to 2011. Patients were more likely to be white (82.0%) and married (53.6%). The most common histopathological subtype of all patients was diffuse large B-cell lymphoma (DLBCL, 61.6%), followed by follicular lymphoma (FL, 13.0%), Burkitt lymphoma (BL, 5.8%), mucosa-associated lymphoma (MALT, 5.0%), small B lymphoma (SBL, 1.3%), and T cell lymphoma (TCL, 1.0%). The primary sites of most patients are in the ovary (38.7%) and cervix uteri (20.9%). According to Ann Arbor Stage, most patients were categorized as stage I (45.1%), followed by stage IV (31.9%), stage II (17.3%), and stage III (5.7%).

The overall diagnosis age is 55.3 years, but the age of diagnosis was lower in BL (33.9 years). And the mean overall survival of BL is the shortest among the B-cell lymphoma (Table 3). Among primary ovary lymphoma, 44.8% of patients are in stage IV of Ann Arbor Stage, but the median overall survival is the longest (121months) (Table 4). DLBCL was the most common histopathological subtype in all primary sites, but it was minor in primary vulva lymphoma (47,2%) (Table 5).

Survival Analysis

The Kaplan-Meier method was used to evaluate the OS and DSS among all patients (Figure 2). The OS and DSS increase over time and decrease with age significantly. Patients younger and diagnosis later seem to have a better prognosis (Figure 3 and Figure 4). Race has no impact on survival, but marital status has an impact on survival significantly. Patients widowed or separated had the shorter OS and DSS than others (Figure 4). According to tumor characteristics, pathological type and Ann Arbor Stage, rather than the primary site, were respectively related to the outcome of PLFGT patients. Stage IV patients with TCL had the worse OS and DSS significantly (Figure 5). The Kaplan-Meier curves for the treatment strategy are presented in Figure 6. OS and DSS improved significantly, but it was various by treatment strategy.

Multivariable Cox regression analysis and Nomogram

Multivariate Cox analysis was performed to identify the prognostic factors associated with the OS and DSS in patients and showing that age, histological type, Ann Arbor stage, and treatment strategy were independent prognostic factors (Table 6). Patients who received a combination of surgery and radiotherapy had the lowest HR for DSS of 0.071 (95% CI,0.009–0.560; *P*=0.012), but it was not significant in OS.

Nomograms for predicting 1-, 5- and 10-year OS and DSS were established based on the results of multivariate Cox analysis in the training dataset (Figure 7). The C-index for nomogram of OS was 0.759 (95% CI 0.731–0.788) in the training group and 0.789 (95% CI 0.754 - 0.825) in the validation group. For nomogram of DSS, The C-index was 0.752 (95% CI 0.717 - 0.788) in the training group and 0.823 (95% CI 0.782 - 0.866) in the validation group. The C-index indicates that all models were reliable. The calibration curve revealed high favorable consistency between the predicted and observed outcomes, indicating that the nomograms could be predictive accuracy (Figure 8 and Figure 9).

Performance of the nomogram in stratifying risk

617 patients were stratified into the high-, middle- and low-risk groups based on total scores of OS using X-tile software. The cutoff values were 101 and 135. Patients at high-risk exhibited a significantly more inferior OS compared to those at low-risk (Figure 10).

Discussion

PLFGT is extremely rare and most studies at present are case reports[11]. There is lacking prognostic analysis for PLFGT due to the low incidence and significant heterogeneity. Seer database is suitable for the study of PBL for its large sample size. So, we conducted this study based on the seer database to analyze the epidemiological trend and established nomograms to predict the prognosis of PLFGT.

Although PLFGT is exceptionally uncommon, our study showed that its incidence has increased in the last 40 years, especially in the period from 1997 to 2007. It is speculated that the causes of this increase include the rise of infectious factors such as the human immunodeficiency virus, the development of immunosuppressive therapy, the additionof the environmental exposure to pesticides and pollutants, and the improvements the diagnostic techniques. [12]. Primary breast lymphoma also occurs in females commonly, but the prognosis of PLFGT is better than primary breast lymphoma [13]. Researchers suspect that hormonal stimulation could potentially influence the growth of PLFGT lesions as primary breast lymphoma[14]. But this has not been confirmed at present.

The clinical manifestations of PLFGT lack specificity[6]. ‘B symptoms’ were uncommon at diagnosis compared with other lymphomas[15]. Some patients are even asymptomatic[16]. Therefore,lymphoma lesions are commonly misdiagnosed, causing the delay in diagnosis and reducing the therapeutic efficacy. Diagnostic imaging is essential for the correct diagnosis of pelvic masses suspected of gynecological lymphoma, but a definite diagnosis requires biopsy with histopathological evaluations and immunophenotyping[17]. Previous studies showed no lesions were detected in the diagnostic curettage for uterine lymphoma, and cervical lymphoma rarely invaded the mucosa, so deep-tissue aspiration biopsy is needed[18, 19]. The prospective diagnosis of lymphoma avoids unnecessary surgery and enables the immediate institution of chemotherapy or radiation therapy[20, 21].

The incidence of PLFGT rises with age in our research, which indicates a long-term accumulated risk factors plays a vital role in the cause of PLFGT. The median age of overall patients was 55 years in our research, but various among the different primary sites and histopathological types[7]. Patients with the primary site in the ovary and cervix uteri tended to present younger than others in our cohort. Previous research also suggest that lymphomas of uterine, vaginal, and vulvar tend to occur in elder women[22, 23]. Primary uterine lymphomas occur in postmenopausal patients commonly but occasionally occur in women in their 20s or 30s[24, 25]. But cervical lymphomas are inclined to present in premenopausal women[26]

Consistent with the most research, DLBCL was the most common type in the primary lymphoma of the female genital tract [27]. Farid Kosari et al. found that the incidence of DLBCL in the vulva was lower than lymphoplasmacytic lymphoma [7], which is conflicted with our study. The rate of DLBCL in the vulva was low relatively in our research, but it is still the largest proportion in all pathological types.

Similarly with other extranodal lymphoma, B-cell lymphomas is associated with better prognosis and overall response to treatment than TCL [15]. But it is worth noting that the BL patients has the lowest age of diagnosis and the worst prognosis among the patients of B-cell lymphomas. So, it is exceedingly imperative to distinguish BL [28].

The prognosis of PLFGT is excellent compared to other gynecologic malignancies if diagnosis at early. DSS tends to increase with the year in our study for the alteration of treatment strategies, mainly targeted treatment, which has dramatically improved the prognosis of patients. But there is no recommended treatment strategy of PFGSL at present.

Our research showed that the radiotherapy and/or surgery can prolong DSS, but it is not conducive for prolonging OS. This maybe cause by the damage of surgery and radiotherapy to the organism, although surgery and radiotherapy could reduce the neoplastic mass and the risk of recurrence[29]. Surgery played a crucial role in the treatment many years ago[30]. But more conservative therapies are the mainstay treatment nowadays[10, 19, 31–33]. For young patients, chemotherapy alone was advocated in the earlier stage to preserve reproductive function[17, 31, 34]. Surgery was performed before NHL diagnosis at present[6]. The most frequently used first-line chemotherapy regimen for PFGSL was the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone), which could prevent micrometastasis and preserve fertility[8]. Rituximab, an *anti-CD20* monoclonal antibody, is effective for the treatment of *CD20*-positive B lymphoma. The combination of rituximab and CHOP regimen (R-CHOP) further improved the survival of B-cell lymphoma[6, 35].

The nomogram has been widely used as an essential prediction model to estimate individual survival[36]. But the nomogram for PFGSL patients is lacking for low incidence. Using the SEER database, our study constructed nomograms based on the age, histological type, and Ann Arbor Stage to provide a quantified survival prediction for individual PFGSL patients. The C-index and calibration plots showed excellent predictive performance of the nomograms.

According to the total score of the nomogram, patients were effectively divided into three groups (high-, middle- and low-risk groups) with the significant OS, which could assist clinicians in enabling personalized treatment.

However, the present study had several limitations. First, this stud is a retrospective study with inevitable inherent bias. Second, some potential independent prognostic variables, such as several biomarkers, B symptoms, and IPI, lacked in the SEER database. Third, the SEER database had no precise data on treatment. Thus, the therapeutic strategy was not included in the construction of nomograms. Therefore, high-quality studies with a larger sample size in future clinical work are indispensable. Despite these

limitations, the SEER database remains a valuable resource in studying rare tumors for its large population. Our research still provided helpful information on the incidence, prognostic factors, and survival for PFGSL.

Conclusion

The incidence of PFGSL has increased in the past 40 years. The present study established and validated a nomogram that could accurately evaluate 1-, 5-, and 10- year OS and DSS for patients with PFGSL. This predictive model could assist clinicians to identify patients at high-risk and choose the optimal individualized treatments for patients.

Abbreviations

BL: Burkitt Lymphoma; C-index: concordance index; CI: confidence interval; DSS: disease-specific survival; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HR: hazard ratio; IPI: international prognostic index; MALT: mucosa-associated lymphoma; NHL: non-Hodgkin lymphoma; OS: overall survival; PLFGT: primary lymphoma of the female genital tract; SBL: small B lymphocytic; SEER database: Surveillance, Epidemiology, and End Results database; TCL: T cell lymphoma;

Declarations

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 LJW: conception of the work, data collection, data analysis, and drafting the article; MSD 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.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Please contact the author for data requests.

Consent for publication

Not applicable.

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Figures

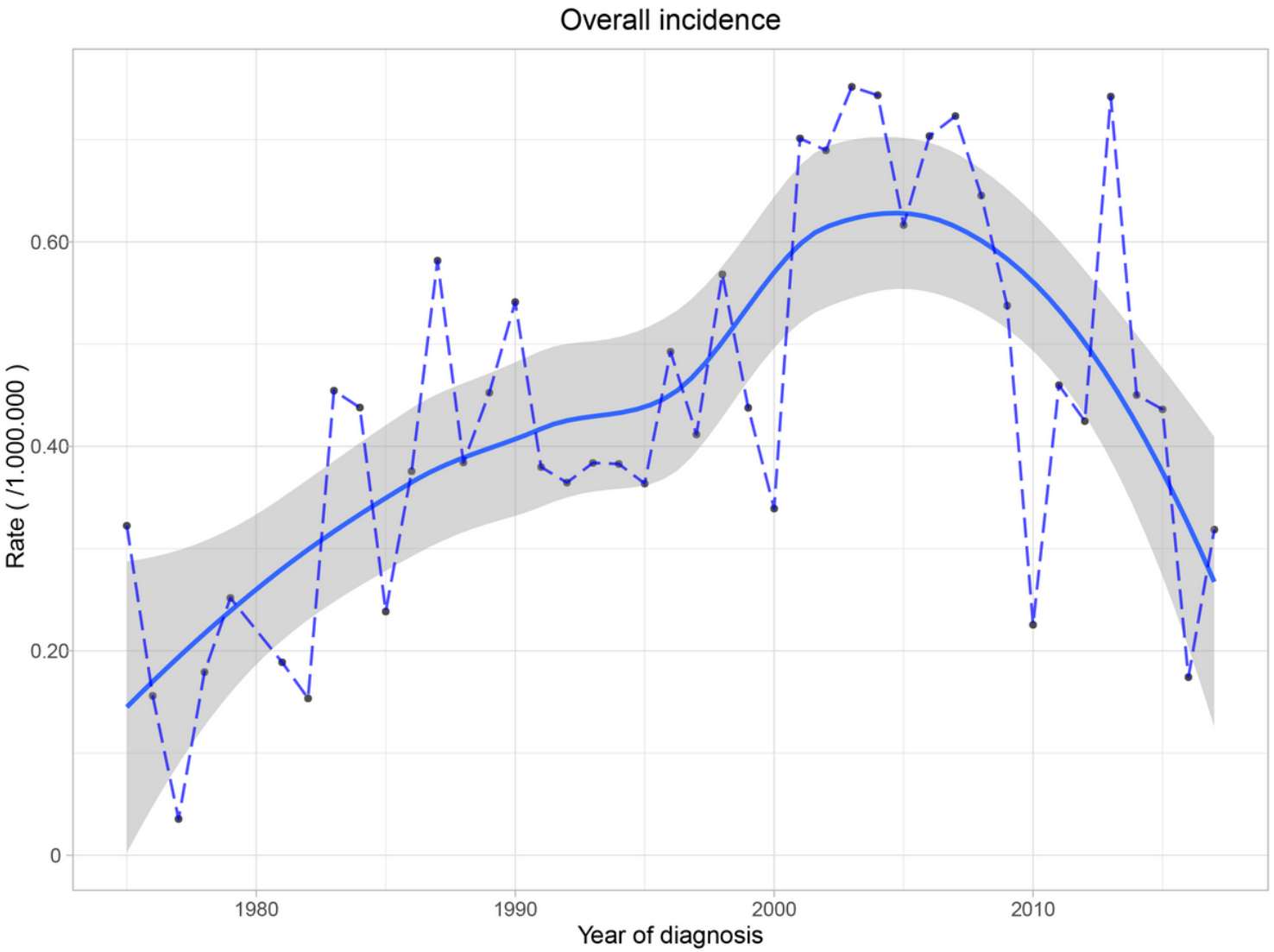

Figure 1

Overall incidence of PFGSL from 1975 to 2017 adjusted to the 2000 standard US

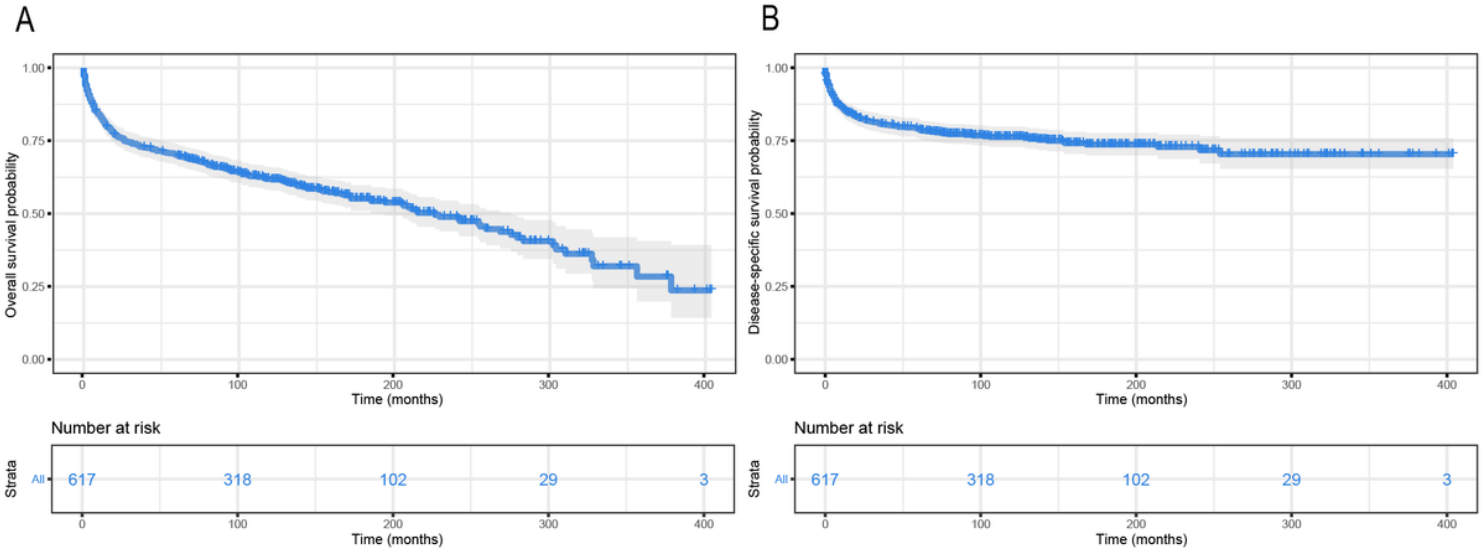

Figure 2

Survival analysis of PFGSL for all patients: (A) OS; (B) DSS.

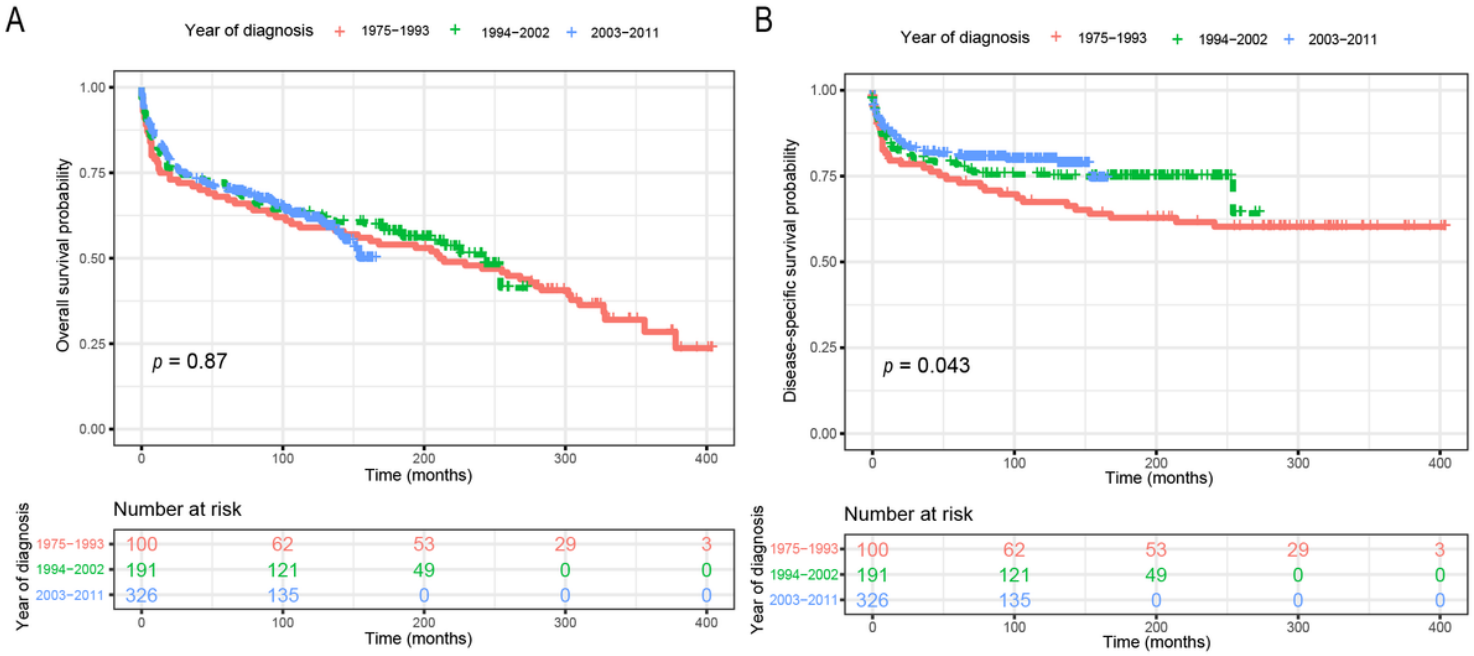

Figure 3

Survival analysis of PFGSL according to years of diagnosis: (A) OS; (B) DSS.

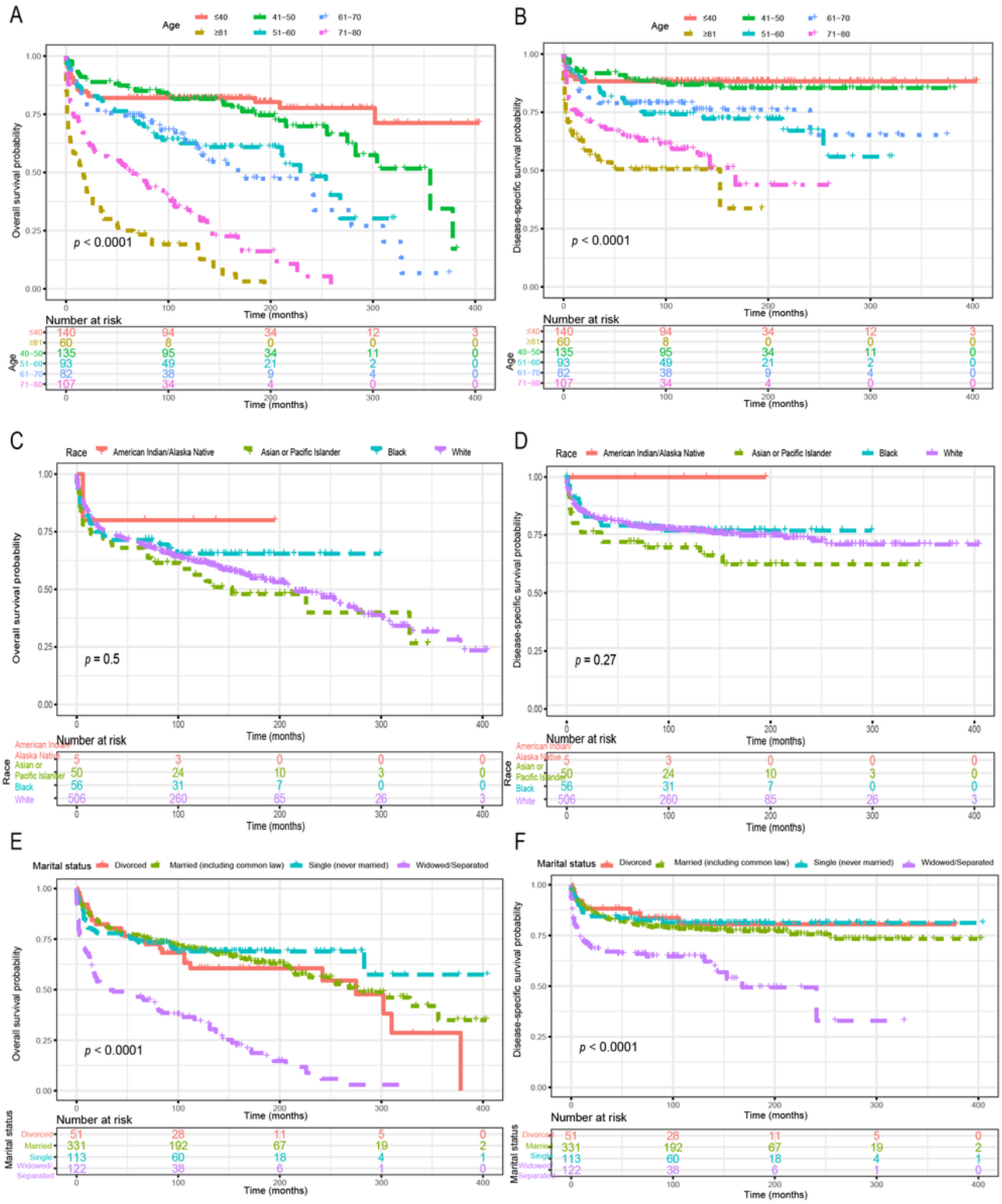

Figure 4

Overall survival of PFGSL according to (A) age, (C) race, and (E) marital status. Disease-specific survival of PFGSL according to (B) age, (D) race, and (F) marital status.

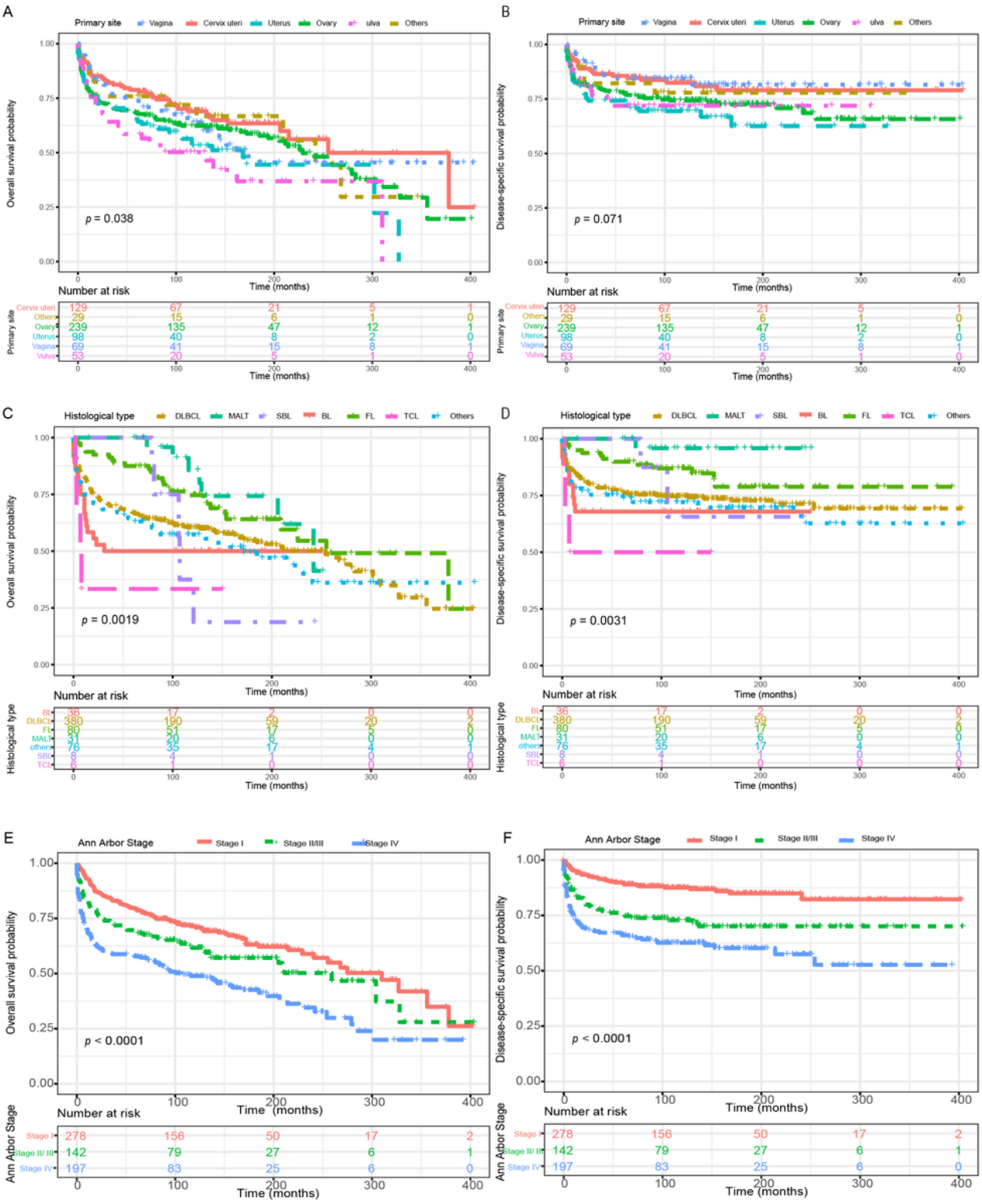

Figure 5

Overall survival of PFGSL according to (A) primary site, (C) histological type and (E) Ann Arbor Stage. Disease-specific survival of PFGSL according to (B) primary site, (D) histological type and (F) Ann Arbor Stage

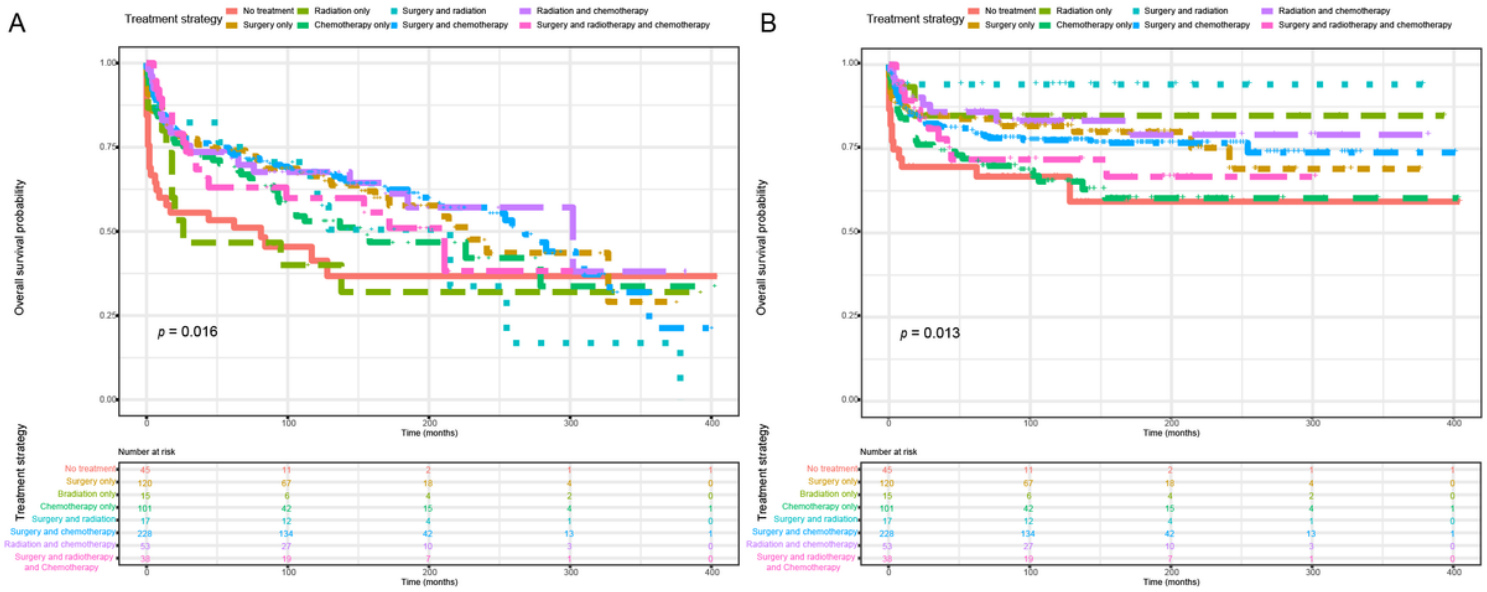

Figure 6

Survival analysis of PFGSL according to treatment strategy: (A) OS; (B) DSS.

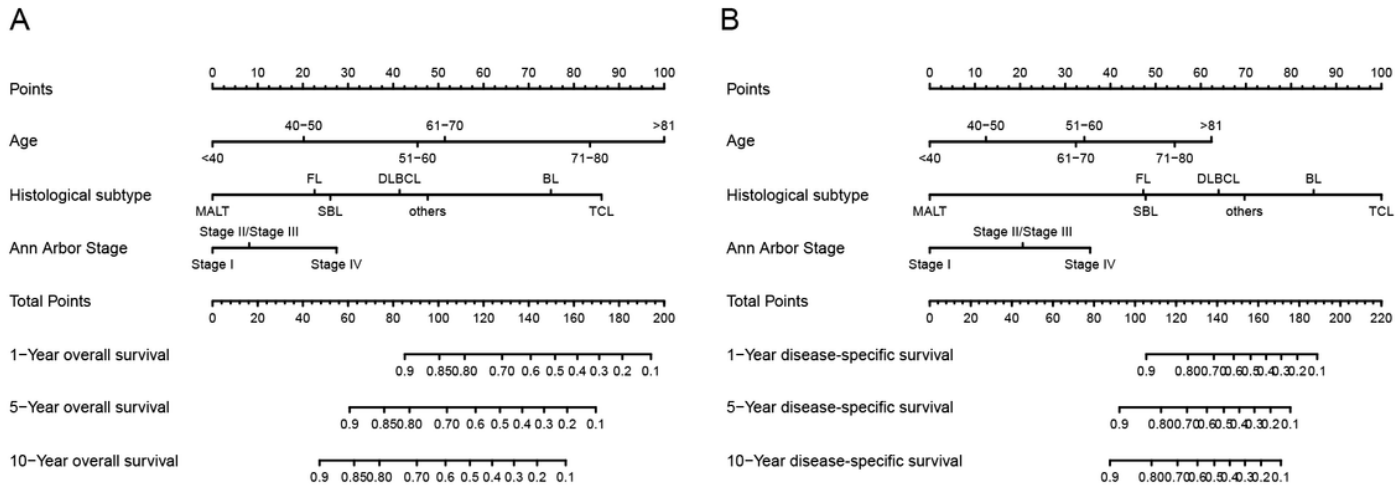

Figure 7

Nomograms to predict (A) overall survival and (B) disease-specific survival for patients with PFGSL

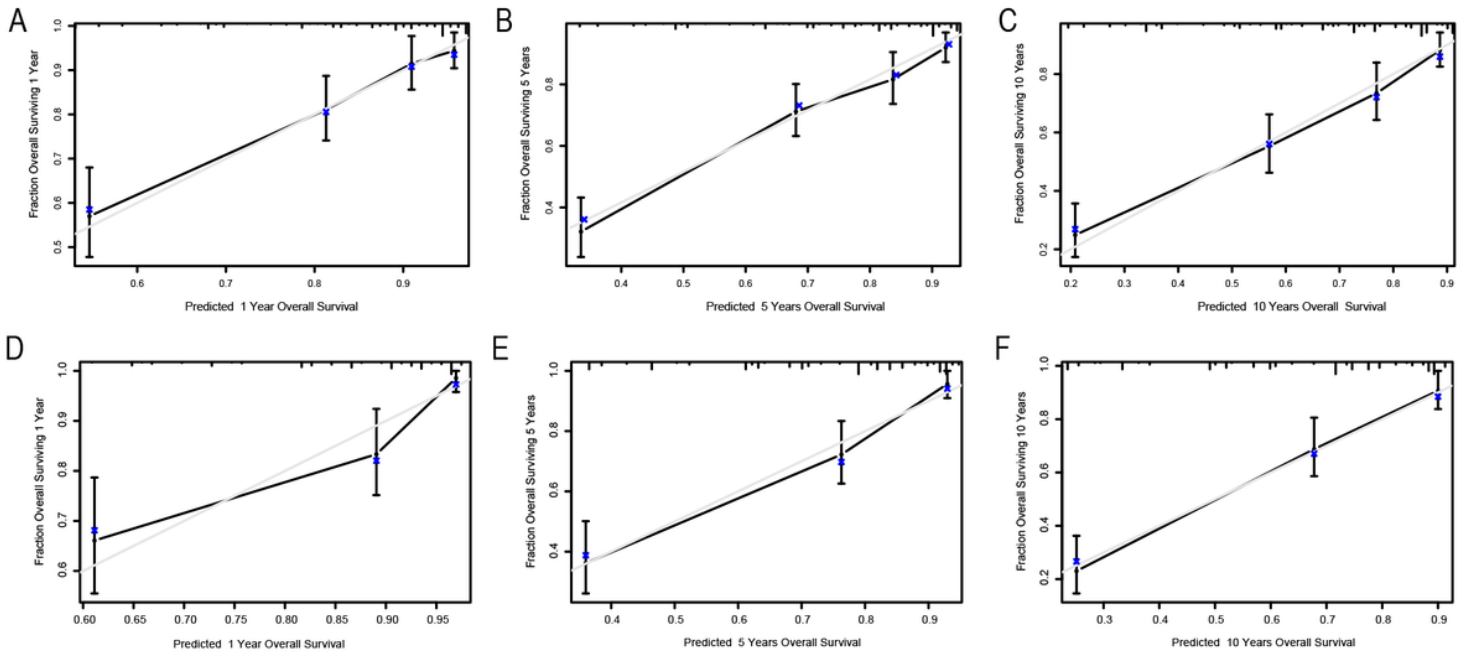

Figure 8

Calibration curves of the nomogram for overall survival in training set (A-C) and validation set (D-E).

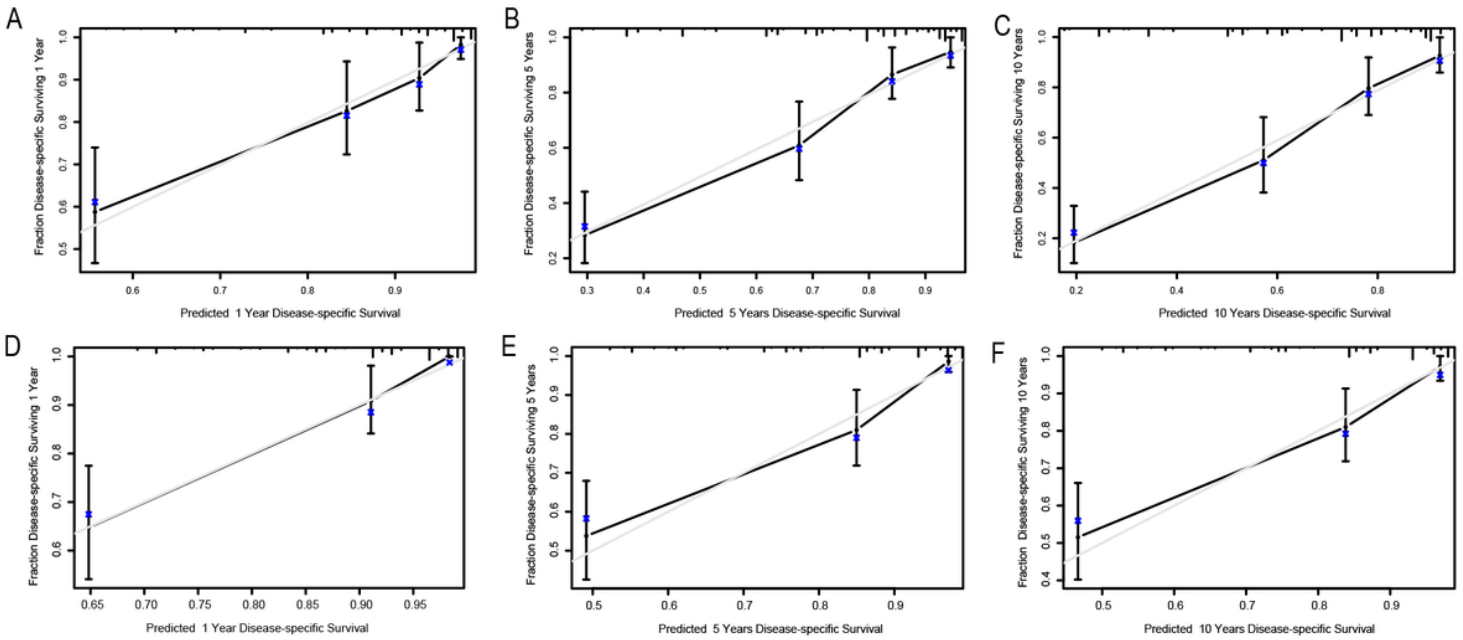

Figure 9

Calibration curves of the nomogram for disease-specific survival in training set (A-C) and validation set (D-E).

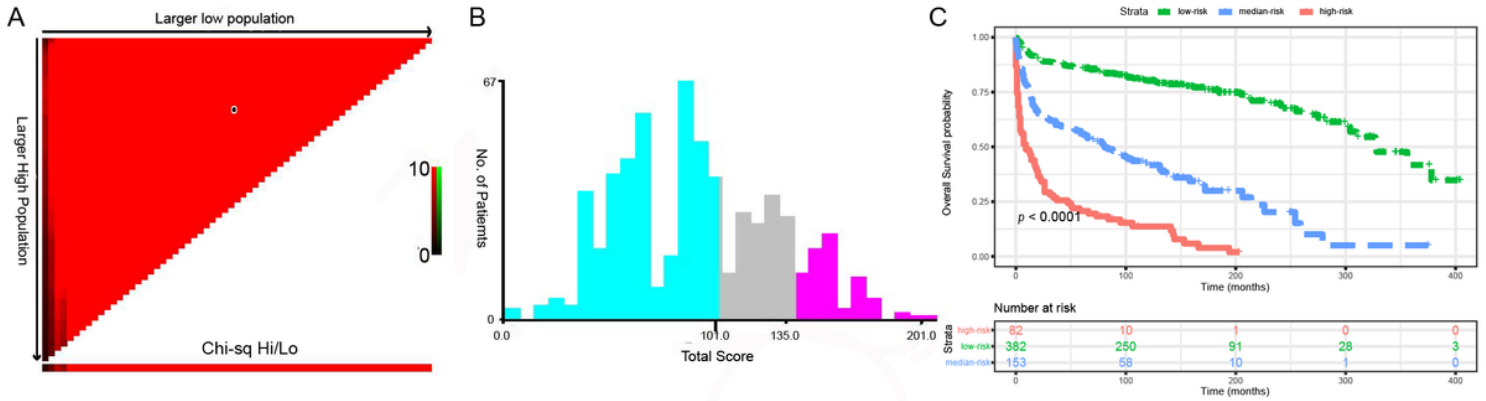

Figure 10

Cut-off values calculated by X-tile (A) and (B). Overall survival of PBL stratified by risk (C).