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Original Article

Prognostic nomogram for primary splenic lymphoma: a SEER database-based study

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Abstract: This study aimed to establish a nomogram model based on the clinicopathological factors affecting the prognosis of patients with primary splenic lymphoma (PSL) to predict the overall survival (OS) and cancer-specific survival (CSS) of patients. A total of 4074 patients diagnosed with PSL were included in this study. Among them, 4052 cases from the SEER (Surveillance, Epidemiology, and End Results) database were randomized into a training set and an internal validation set in a 7:3 ratio. Another 22 patients from the First Affiliated Hospital of Xi'an Jiaotong University were used as an external validation set. The prognostic factors affecting the OS and CSS of patients were analyzed using univariate and multivariate Cox regression models. Survival analysis was performed using Kaplan-Meier (KM) method and compared by Log-rank test. Then, a nomogram model was established to predict OS and CSS. Finally, the model was validated both internally and externally using the concordance index (C-index), receiver operating characteristic curve (ROC), and calibration curve to evaluate its predictive value, and the decision curve analysis (DCA) was conducted to assess its clinical utility. Our results showed that the model displayed a good prediction ability. In the training set, the OS rates at 1, 3, and 5 years were 85.9%, 75.8% and 70.1%, respectively, while the CSS rates at 1, 3, and 5 years were 91.9%, 86.2% and 82.3%, respectively. Predictors in the prediction model of OS included age, sex, marital status, Ann Arbor stage, histology, surgery, chemotherapy and year at diagnosis. On the other hand, predictors in the model of CSS included age, Ann Arbor stage, histology, chemotherapy, and year at diagnosis. Internal and external validation of the nomogram model showed that the C-index for predicting OS was 0.678 (0.662, 0.694) in the training set, 0.672 (0.648, 0.696) in the internal validation set, and 0.704 (0.565, 0.843) in the external validation set; the C-index for predicting CSS was 0.685 (0.661, 0.709) in the training set, 0.683 (0.650, 0.716) in the internal validation set, and 0.676 (0.488, 0.864) in the external validation set. The calibration curves for several groups showed good consistency, and DCA suggested its clinical usability. In conclusion, the nomogram constructed in this study has a good predictive value for the survival of patients with PSL, and can be a clinically applicable and practical prediction tool, facilitating rapid and accurate individualized predictions of the patient survival.

Keywords: Primary splenic lymphoma, overall survival, cancer-specific survival, nomogram

Introduction

Primary splenic lymphoma (PSL) is a rare tumor that occurs in the spleen, usually without involvement of extra splenic organs and lymph nodes. It may occur in less than 2% of all lymphomas and 1% of all non-Hodgkin lymphomas [1, 2]. PSL are mostly non-Hodgkin lymphomas. The incidence is higher in men than in women. Moreover, the age of onset is usually over 50 years old, and the median age at diagnosis is 69 years old [3]. Splenic marginal zone lymphoma (SMZL) is the most common histological subtype [4]. PSL is rare, accounting for only about 1% of all malignancies, but it ranks first among primary malignancies of the spleen [5]. Moreover, the incidence of splenic lymphoma has gradually increased in recent years [6, 7].

The cause of PSL has not been fully elucidated, and infection is the primary related factor, mostly hepatitis C virus (HCV) infection [8].

Some case reports and retrospective studies suggest an association between HCV infection and the development of splenic B-cell lymphoma, and PSL does occur in patients with chronic liver disease caused by HCV infection, suggesting a non-accidental link between PSL and HCV infection [9]. In southern Italy, the frequency of HCV infections associated with SMZL is higher, where it has been detected in up to 3.1% of cases [10]. Therefore, HCV infection may play an important role in the development of splenic lymphoma, although the exact mechanism of malignant lymphoma development after HCV infection is unknown. In addition, some chronic diseases of the spleen, such as chronic recurrent infections, may also be related to the development and progression of splenic lymphoma.

Nonspecific clinical manifestations of PSL include left upper quadrant pain, weight loss, fatigue, anorexia, fever, and night sweats [4, 11]. A small number of patients may also present with an acute abdomen, pleural effusion, and dyspnea. Its specific clinical manifestations are mainly caused by tumor cells invading the surrounding organs of the spleen, such as the stomach, colon, and pancreas. The clinical manifestations of PSL are ambiguous, but it can be accompanied by severe complications such as hypersplenism and spleen rupture. The nonspecific clinical presentation of PSL makes diagnosis difficult. The Ann Arbor clinical staging protocol is often used to divide lymphoma into 4 stages according to the degree of lymph node involvement. Ahmann stages are more granular, with PSL being divided into 3 stages depending on where the lesion is involved. Stage I refers to lesions only in the spleen; stage II refers to spleen and hilar lymph node involvement; stage III refers to extra splenic lymph node or liver involvement [12].

Treatment for PSL includes observation (active surveillance or wait-and-see), splenectomy, rituximab, and immunochemotherapy. Due to the rarity of this disease, no clear management guidelines have been established.

However, there are mostly case reports but few clinical reports on the occurrence of primary tumors in the spleen. Due to its rarity, there is a lack of information on the clinicopathological features of PSL and its prognosis. The existing reports are mostly case reports and small-scale retrospective studies, which fail to provide consistent and accurate conclusions [13, 14]. In addition to the limit number of clinical studies, there is also no large-scale systematic analysis. Therefore, it is of great clinical value to study the impact of clinical treatment patterns on the long-term survival of patients through analyzing large-sample clinical databases, which may provide high-level clinical evidence for the formulation of standard treatment patterns.

As a clinical prediction tool, nomogram can generate a clinical profile by integrating different prognostic factors, which could aid in predicting patient outcomes and facilitate the selection of appropriate treatment options [15]. This study aimed to reveal the prognostic factors affecting PSL through analyzing a large sample database, and to establish a nomogram to predict patient survival and prognosis.

Materials and methods

Data sources

The research data of training set and internal validation set for this study are from the Surveillance, Epidemiology, and End Results (SEER) database, one of the most authoritative cancer statistical databases in the United States. SEER database collects information on the incidence, mortality, and prevalence of malignant tumors for approximately 30% of the US population. Specifically, the available data include demographic data, patient ID, personal information, primary tumor location, tumor size, tumor code, treatment plan, cause of death and so on, providing sufficient information for research on malignant tumors and rare tumors [16, 17]. The SEER database has a large sample size, high quality, and strong statistical power, offering data with high clinical reference value for tumor-related research. As the SEER database is an open-access resource, with anonymized patient information, this study does not require ethical review or informed consent. The data of the external validation set in this study was obtained from the First Affiliated Hospital of Xi'an Jiaotong University.

Patients

Firstly, according to the ICD-O-3, using histological codes (9590-9591, 9596, 9650-9653, 9663-9664, 9667, 9670-9671, 9673, 9675,

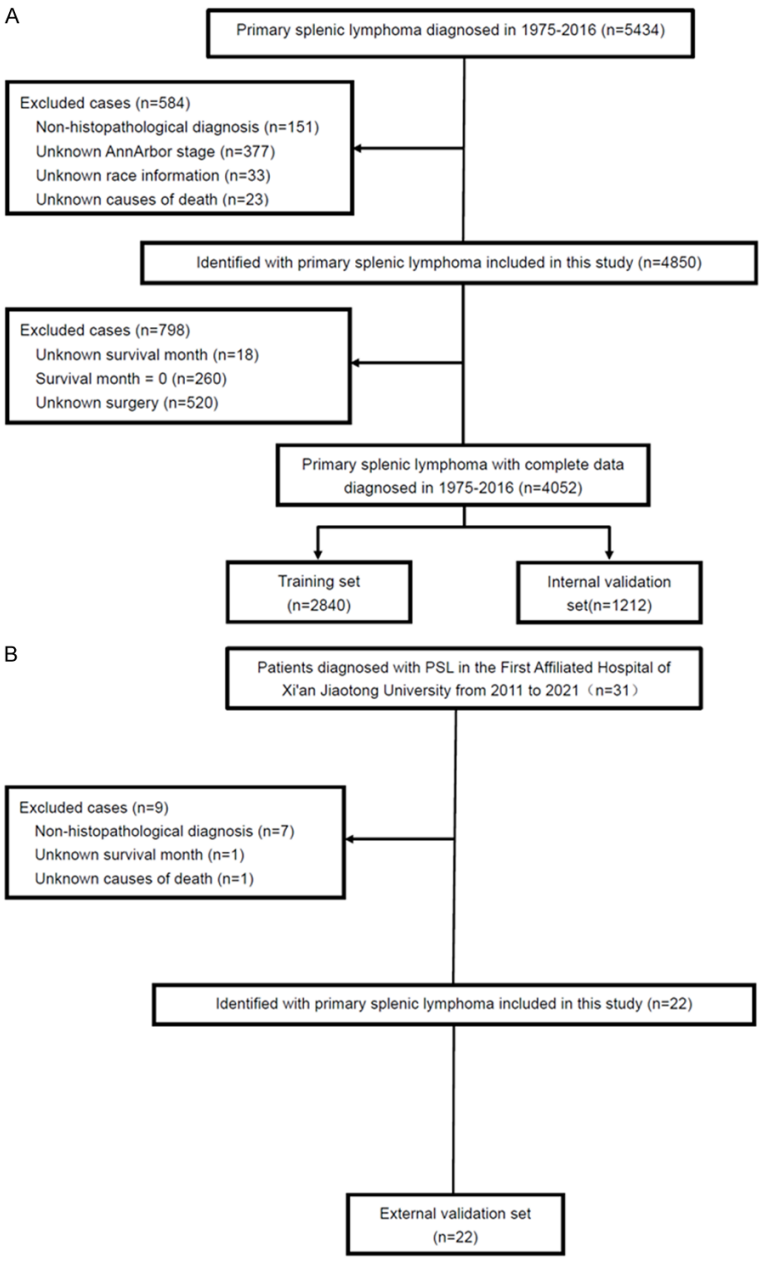

Figure 1. Patients' inclusion and exclusion flow chart. A. 4052 patients with PSL from the SEER database were divided into a training set (n = 2840) and an internal validation set (n = 1212); B. 22 patients with PSL from the First Affiliated Hospital of Xi'an Jiaotong University, were the external validation set. Abbreviation: PSL, primary splenic lymphoma.

9680, 9684, 9687-9691, 9695, 9698-9699, 9702, 9705, 9712, 9714, 9716, 9719, 9724, 9726-9727) and major anatomical sites (C42.2), we collected data of patients with PSL from January 1975 to December 2016 in the SEER database. We extracted data including age, sex, race, marital status, AnnArbor stage, histology, surgery, radiation therapy, chemotherapy, year at diagnosis, follow-up information, and cause of death.

Meanwhile, we collected data of patients diagnosed with PSL in the First Affiliated Hospital of Xi'an Jiaotong University from 2011 to 2021, including sex, age, hospitalization number, AnnArbor stage, histology, surgical method, radiotherapy, and chemotherapy status, etc. Personal information of all patients in this study was excluded.

Survival data included overall survival (OS), which is defined as from the date of diagnosis to the last follow-up or death from all causes, and cancer-specific survival (CSS), which refers to death from the disease.

Inclusion and exclusion criteria

The inclusion criteria of this study were: (1) patients who were diagnosed with PSL by histopathological examinations; (2) patients with complete data, including clear treatment and surgical methods. The exclusion criteria were: (1) patients with secondary splenic lymphoma; (2) patients whose diagnosis was confirmed by autopsy; (3) patients without known survival information or recorded survival time of 0 days; (4) patients whose cause of death was unknown. The patient inclusion and exclusion process is summarized in **Figure 1**.

Statistical analyses

In this study, Excel 2019 software was used to organize the data. SPSS18.0 software, R4.1.1

software, and X-tile software were used for statistical analysis. In prognostic analysis, the survival curve of the survival rate was drawn by the Kaplan-Meier method, and the differences among the factors were calculated by the Log-rank test. For the test of continuous variable (age), the optimal cut-off value was obtained by X-tile software. Cox regression model was used for univariate analysis and multivariate analysis, and the independent factors affecting the OS rate and CSS rate were obtained. The hazard ratio (HR) and 95% confidence interval (CI) of each variable were also determined. In the relevant statistical analysis, the statistical significance level was set at $P<0.05$.

We used the random sampling function in R software version 4.1.1 to randomly divide patients into training and validation groups. At the same time, we used the log-rank test in the "survival" package to screen prognostic factors, and then performed Cox proportional hazards regression model analysis (constructed using the training set data). In addition, we used "rms", "timeROC" and "nomogramFormula" packages to build a nomogram, calculate the C-index, and draw receiver operating characteristic (ROC) curves to evaluate the discriminative ability (discrimination) of the model. Then, the clinical utility of the nomogram was evaluated by decision curve analysis (DCA). Finally, the Bootstrap method (the number of self-sampling times B = 1000) was used for internal and external validation in the data sets.

In an ideal calibration curve, where the predicted and actual observed values are equal, the curve would be infinitely close to the ideal 45° slope. The C-index, similar to the area under the ROC curve (AUC), was used to assess the predictive value of the nomogram, with a minimum value of 0.5 and a maximum value of 1.0. A larger C index indicates higher predictive value.

Results

Patient characteristics

Table 1 shows the demographic and clinicopathological characteristics of all three cohorts, including training set (n = 2840), internal validation set (n = 1212), and external validation set (n = 22). In the training set, there were 1456 males and 1384 females, with a male-to-female ratio of approximately 1.0:1.0; 1405 (49.4%) were aged <67 years old, 867 (30.5%) were 67-77 years old, and 568 were ≥78 years old (20.1%); 1175 cases (41.4%) with onset time during 1998-2006, 1665 cases (58.6%) during 2007-2015; 2549 cases (89.7%) of white people, 171 cases (6.0%) of black people, 120 cases (4.3%) of other or unknown; 1703 cases (59.9%) married, 993 cases (34.9%) unmarried, 144 cases (5.2%) unknown; 1173 cases (41.3%) of AnnArbor stage I-II, AnnArbor stage III-IV 1667 cases (58.7%); 90 cases (3.2%) received radiotherapy, 2750 cases (96.8%) not; 1478 cases (52.1%) received chemotherapy, 1362 cases (47.9%) not. Interestingly, nearly half (49.5%) of the patients in the training set had SMZL pathology, compared to only 18.2% of patients with SMZL in the external validation set. In addition, only 52.7% of patients in the training set underwent surgery, while all patients in the external validation set underwent surgery. The baseline characteristics of the training set and the validation sets are shown in **Table 1**.

Analysis of influencing factors of OS

The mean follow-up period of the 4052 patients from the database was 100.3 months (0-227 months). Among them, a total of 1787 patients died, including 793 cancer-specific deaths and 994 deaths from other causes. The OS of patients at 1, 3, 5 and 10 years were 85.9%, 75.8%, 70.1% and 59.9%, respectively.

Univariate Log-rank test analysis was performed on the patients in the training set, and the results showed that age, sex, marital status, AnnArbor stage, histology, surgery, and year at diagnosis were associated with the OS ($P<0.05$). Other factors, such as race and radiotherapy, were not associated with the OS of PSL ($P>0.05$) (**Table 2**; **Figures 2** and **3**).

Based on the results of univariate analysis, a multivariate Cox regression analysis was further conducted. The analysis factors included age, sex, race, marital status, AnnArbor stage, histology, surgery, radiotherapy, chemotherapy and year at diagnosis. The results showed age, sex (HR = 0.711, 95% CI = 0.631-0.799, P< 0.001), marital status, AnnArbor stage (HR = 1.209, 95% CI = 1.069-1.369, P = 0.002), histology (HR = 1.298, 95% CI = 1.143-1.472,

Table 1. Demographic and clinicopathologic characteristics of the training and validation sets

Characteristic	Patients					
	Training set (n = 2840)		Internal validation set (n = 1212)		External validation set (n = 22)	
	Case No. (n)	%	Case No. (n)	%	Case No. (n)	%
Age (years)						
<67	1405	49.4%	584	48.2%	17	77.3%
67-77	867	30.5%	362	29.9%	4	18.2%
≥78	568	20.1%	266	21.9%	1	4.5%
Race						
White	2549	89.7%	1085	89.5%	0	0%
Black	171	6.0%	69	5.7%	0	0%
Other	120	4.3%	58	4.8%	22	100%
Sex						
Male	1456	51.2%	609	50.2%	10	45.5%
Female	1384	48.8%	603	49.8%	12	54.5%
Marital status						
Married	1703	59.9%	723	59.7%	22	100%
Unmarried	993	34.9%	426	35.1%	0	0%
Unknown	144	5.2%	63	5.2%	0	0%
Ann Arbor stage						
I-II	1173	41.3%	506	41.7%	6	27.3%
III-IV	1667	58.7%	706	58.3%	16	72.7%
Histology						
SMZL	1407	49.5%	577	47.6%	4	18.2%
Non-SMZL	1433	50.5%	635	52.4%	18	81.8%
Radiotherapy						
Yes	90	3.2%	40	3.3%	1	4.5%
No	2750	96.8%	1172	96.7%	21	95.5%
Surgery						
Yes	1498	52.7%	642	53.0%	22	100%
No	1342	47.3%	570	47.0%	0	0%
Chemotherapy						
Yes	1478	52.1%	606	50.0%	13	59.1%
No	1362	47.9%	606	50.0%	9	40.9%
Year at diagnosis						
1998-2006	1175	41.4%	498	41.1%	0	0%
2007-2015	1665	58.6%	714	58.9%	22	100%
Median follow-up months	56		55		22	
No. of death (%)	1243 (43.8%)		544 (44.9%)		8 (36.4%)	
5-year CSS rate	82.3%		84.7%		68.2%	

P<0.001), surgery (HR = 1.021, 95% CI = 0.903-1.155, P<0.001), chemotherapy (HR = 0.865, 95% CI = 0.767-0.975, P = 0.018) and year at diagnosis (HR = 0.744, 95% CI = 0.658-0.842, P<0.001) were associated with the OS of PSL (P<0.05). As shown in **Table 3**, factors, such as unmarried, AnnArbor stage III-IV, non-SMZL, no surgery, and earlier year at diagnosis were associated with a worse prognosis. In addition, the age at diagnosis younger than 67 years, female, chemotherapy, and diagnosis during 2007-2015 were associated with a better prognosis. However, with or without radiotherapy had no significant impact in the progno-

Table 2. Overall survival rates and univariate analysis of clinicopathological factors in primary splenic lymphoma

Characteristic	No. (%)	Overall survival rates (%)				Univariate analysis	
		1-year	3-year	5-year	10-year	Chi-square	P
Total	2840 (100%)	85.9	75.8	70.1	59.9		
Age (years)						407.01	<0.001
<67	1405 (49.4%)	90.5	83.4	80.1	73.1		
67-77	867 (30.5%)	86.5	75.3	69.1	56.3		
≥78	568 (20.1%)	73.9	57.7	47.1	33.1		
Race						0.871	0.647
White	2549 (89.7%)	86.4	76.3	70.5	59.9		
Black	171 (6.0%)	80.1	69.6	66.1	58.5		
Other	120 (4.3%)	85.0	73.3	66.7	61.7		
Sex						10.94	<0.001
Male	1456 (51.2%)	83.5	73.3	67.4	57.1		
Female	1384 (48.8%)	88.5	78.5	72.8	63.1		
Marital status						47.01	<0.001
Married	1703 (59.9%)	88.3	79.3	73.9	64.0		
Unmarried	993 (34.9%)	81.7	69.2	62.5	52.5		
Unknown	144 (5.2%)	87.5	80.6	76.4	63.9		
Ann Arbor stage						7.988	0.005
I-II	1173 (41.3%)	87.6	78.3	72.9	63.3		
III-IV	1667 (58.7%)	84.8	74.1	68.1	57.6		
Histology						16.73	<0.001
SMZL	1407 (49.5%)	90.9	81.3	74.8	64.5		
Non-SMZL	1433 (50.5%)	81.1	70.4	65.5	55.5		
Radiotherapy						1.341	0.247
Yes	90 (3.2%)	82.2	71.1	64.4	53.3		
No	2750 (96.8%)	86.1	75.9	70.3	60.2		
Surgery						13.53	<0.001
Yes	1498 (52.7%)	87.7	77.6	72.3	60.7		
No	1342 (47.3%)	84.1	73.8	67.6	59.2		
Chemotherapy						3.682	0.055
Yes	1478 (52.1%)	87.6	78.1	72.3	61.4		
No	1362 (47.9%)	84.2	73.3	67.7	58.4		
Year at diagnosis						22.19	<0.001
1998-2006	1175 (41.4)	84.2	70.4	62.9	44.9		
2007-2015	1665 (58.6%)	87.2	79.6	75.1	70.6		

sis of PSL, which is consistent with the results of univariate analysis.

Analysis of influencing factors of CSS

Among the 2840 patients in the training set, 552 died from PSL. The CSS of patients at 1, 3, 5, and 10 years were 91.9%, 86.2%, 82.3%, and 73.9%, respectively. Univariate analysis showed that age, marital status, AnnArbor stage, histology, surgery, radiotherapy, chemotherapy, and year at diagnosis were associated with the CSS in patients with PSL (P<0.05) (**Table 4**; **Figure 4**).

Based on the results of univariate analysis, further multivariate analysis was conducted. The analysis factors included age, marital status, AnnArbor stage, histology, surgery, radiotherapy, chemotherapy and year at diagnosis. Among them, age, AnnArbor stage (HR = 1.702, 95% CI = 1.408-2.057, P<0.001), histology (HR = 1.793, 95% CI = 1.478-2.176, P<0.001), chemotherapy (HR = 0.688, 95% CI = 0.574-

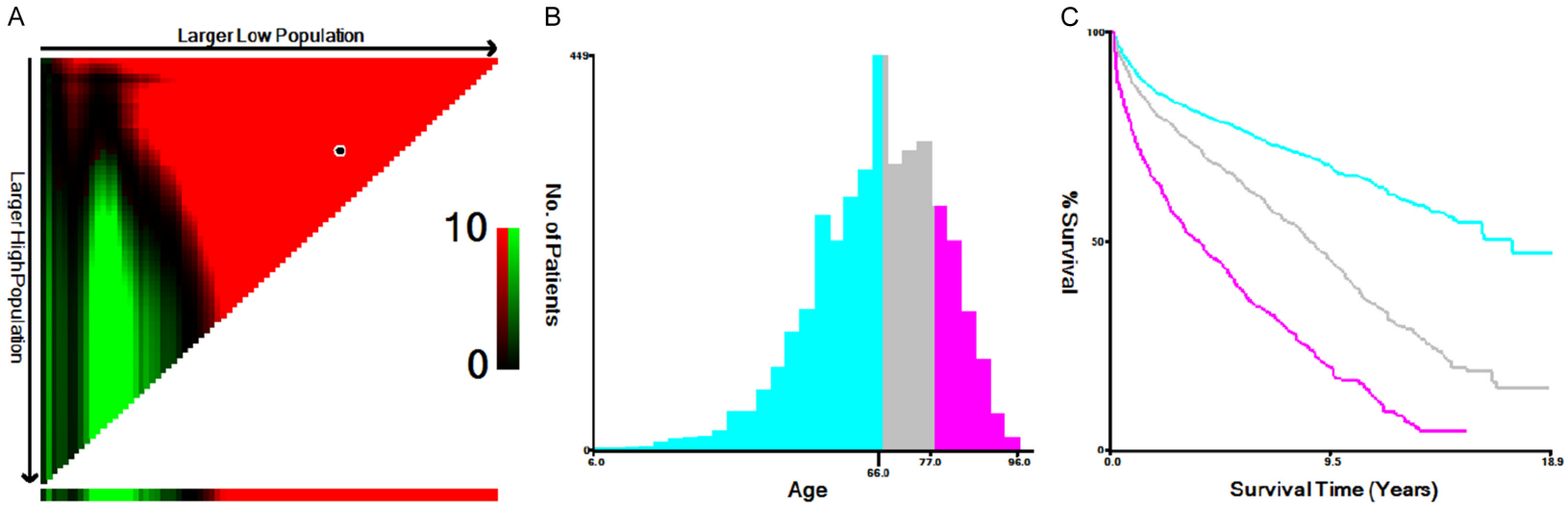

Figure 2. The optimal cut-off value for age in patients with PSL. Abbreviation: PSL, primary splenic lymphoma.

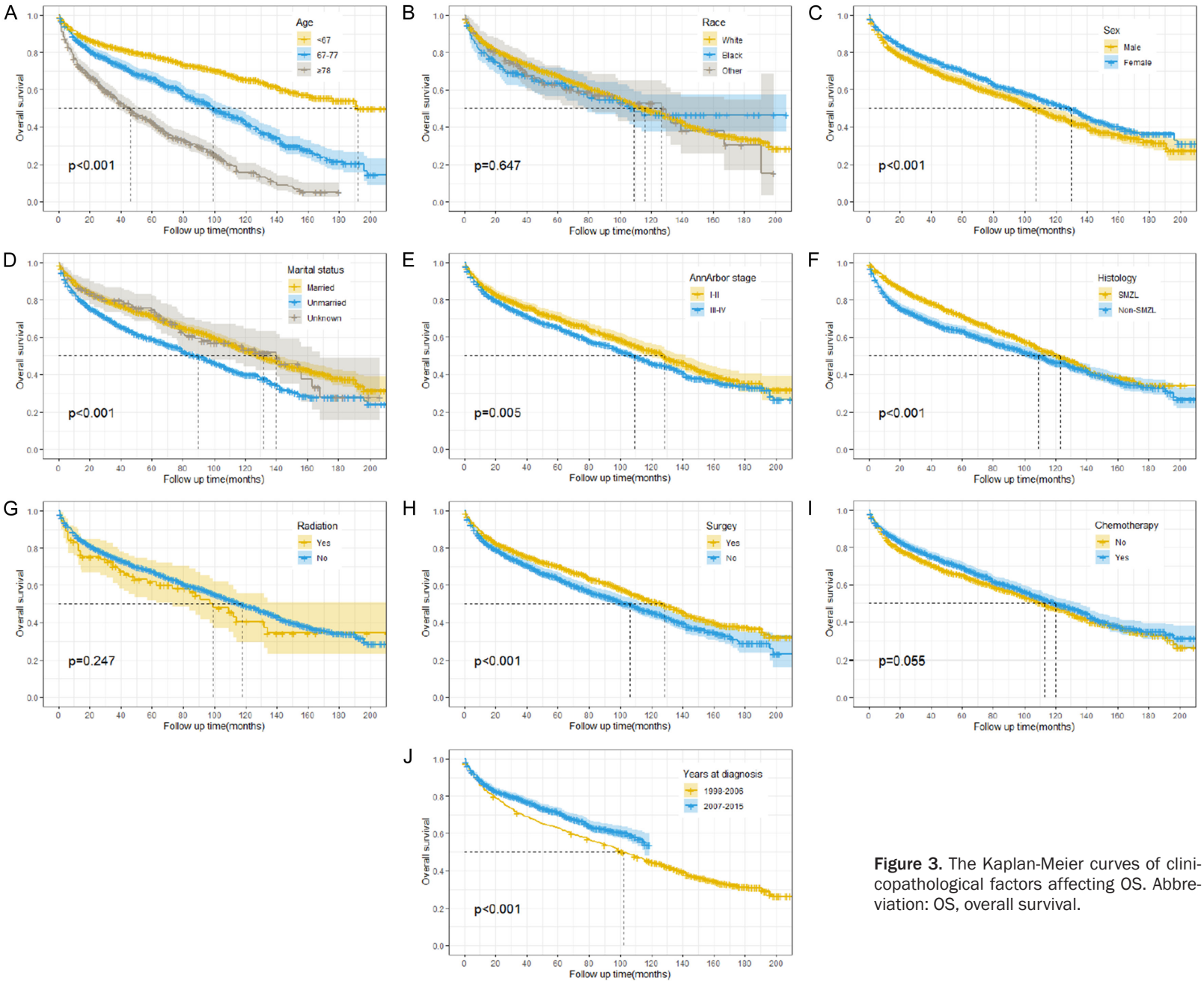

Figure 3. The Kaplan-Meier curves of clinicopathological factors affecting OS. Abbreviation: OS, overall survival.

Table 3. Multivariate analysis of clinicopathological factors affecting overall survival in primary splenic lymphoma

Characteristic	HR	95% Confidence interval		*P* value
		Lower limit	Upper limit	
Age (years)				
<67	1			
67-77	2.083	1.816	2.391	<0.001
≥78	4.117	3.558	4.765	<0.001
Race				
White	1			
Black	1.205	0.944	1.539	0.135
Other	1.236	0.934	1.634	0.138
Sex				
Female:Male	0.711	0.631	0.799	<0.001
Marital status				
Married	1			
Unmarried	1.494	1.322	1.689	<0.001
Unknown	1.105	0.846	1.444	0.464
Ann Arbor stage				
III-IV:I-II	1.209	1.069	1.369	0.002
Histology				
Non-SMZL:SMZL	1.298	1.143	1.472	<0.001
Radiotherapy				
No:Yes	1.013	0.747	1.375	0.933
Surgery				
No:Yes	1.021	0.903	1.155	<0.001
Chemotherapy				
Yes:No	0.865	0.767	0.975	0.018
Year at diagnosis				
2007-2015:1998-2006	0.744	0.658	0.842	<0.001

0.826, P<0.001) and year at diagnosis (HR = 0.678, 95% CI = 0.565-0.813, P<0.001) were found to be significantly associated with the CSS (**Table 5**). Factors, such as age ≥78 years old, unmarried, AnnArbor stage III-IV, non-SMZL cases, were all risk factors for shorter CSS and worse prognosis. In contrast, age younger than 67 years at diagnosis, chemotherapy, and diagnosis during 2007-2015 were associated with better prognosis.

There was no significant difference in the CSS between patients with or without surgery and radiotherapy.

Nomogram for predicting OS and CSS

According to the multivariate Cox regression analysis results, the statistically significant independent prognostic factors affecting OS were integrated to construct a Nomogram. The included prognostic factors included age, sex, marital status, AnnArbor stage, histology, surgery, chemotherapy and year at diagnosis. The prediction results for 3-year and 5-year OS are shown in **Figure 5**.

Based on the results of multivariate analysis, we included independent prognostic factors affecting CSS and constructed a nomogram, including age, AnnArbor stage, histology, chemotherapy, and year at diagnosis. The predicted results are shown in **Figure 6**.

The line segment corresponding to each variable in the figure is marked with a scale, which represents the variable value range, and the length of the line segment reflects the contribution of the factor to the outcome event. The score (points) of each variable under different values were added up to obtain the total score (total points), and the OS or CSS could be obtained by downward projection. The nomogram can transform the complex Cox regression analysis results into a simple visual graph, so that the survival rate of patients can be predicted according to different variables, which helps to improve the prediction accuracy.

Verification of the nomogram

In this study, the Bootstrap method was used for internal and external validation of the nomogram, and the number of self-samplings was 1000. The validation results showed that the C-index for predicting OS was 0.678 (0.662, 0.694) in the training set, 0.672 (0.648, 0.696) in the internal validation set, and 0.704 (0.565, 0.843) in the external validation set. Meanwhile, the C-index for predicting CSS was 0.685 (0.661, 0.709) in the training set, 0.683 (0.650, 0.716) in the internal validation set, and 0.676 (0.488, 0.864) in the external validation set. These results suggest that the nomogram has a good predictive value in both OS and CSS. See **Table 6**.

Table 4. Cancer-specific survival rates and univariate analysis of clinicopathological factor in primary splenic lymphoma

Characteristic	No. (%)	Overall survival rates (%)				Univariate analysis	
		1-year	3-year	5-year	10-year	Chi-square	P
Total	2840 (100%)	91.9	86.2	82.3	73.9		
Age (years)						46.532	<0.001
<67	1405 (49.4%)	93.5	88.7	85.7	79.1		
67-77	867 (30.5%)	92.6	86.1	81.4	70.7		
≥78	568 (20.1%)	86.7	79.3	74.2	61.7		
Race						5.496	0.064
White	2549 (89.7%)	92.3	86.7	82.9	74.3		
Black	171 (6.0%)	87.1	80.7	77.8	71.9		
Other	120 (4.3%)	89.5	81.9	76.8	68.9		
Sex						2.289	0.131
Male	1456 (51.2%)	91.1	84.8	80.6	72.9		
Female	1384 (48.8%)	92.8	87.5	84.0	74.9		
Marital status						28.19	<0.001
Married	1703 (59.9%)	93.6	88.9	85.1	77.3		
Unmarried	993 (34.9%)	88.9	81.2	77.1	66.7		
Unknown	144 (5.2%)	92.9	88.1	87.1	80.5		
Ann Arbor stage						20.751	<0.001
I-II	1173 (41.3%)	94.1	89.4	86.6	79.4		
III-IV	1667 (58.7%)	90.4	83.9	79.4	70.1		
Histology						42.959	<0.001
SMZL	1407 (49.5%)	95.4	91.5	87.6	77.9		
Non-SMZL	1433 (50.5%)	88.4	80.9	77.1	69.8		
Radiotherapy						5.598	0.018
Yes	90 (3.2%)	86.2	77.3	74.1	65.5		
No	2750 (96.8%)	92.1	86.5	82.6	74.2		
Surgery						5.756	0.016
Yes	1498 (52.7%)	93.1	87.3	83.9	75.3		
No	1342 (47.3%)	90.5	84.9	80.5	72.4		
Chemotherapy						31.505	<0.001
Yes	1478 (52.1%)	94.1	89.9	86.3	78.7		
No	1362 (47.9%)	89.5	82.2	78.2	68.9		
Year at diagnosis						22.376	<0.001
1998-2006	1175 (41.4)	90.2	82.5	78.1	69.8		
2007-2015	1665 (58.6%)	93.1	89.1	85.9	-		

The ROC curve was used to evaluate the discriminative ability of nomogram. As shown in **Figure 7** and **Table 7**, the AUC values for predicting 3-year and 5-year OS were 0.692 and 0.695, respectively, in the training set, 0.672 and 0.671 in the internal validation set, and 0.625 and 0.609 in the external validation set. As shown in **Figure 8** and **Table 7**, the AUC values for predicting 3-year, and 5-year CSS were 0.699, and 0.677, respectively, in the training set, 0.691 and 0.652 in the internal validation set, and 0.646 and 0.589 in the external validation set. Both in the training set and validation set, the nomogram showed good predictive value.

The calibration curves of nomogram for predicting 3- and 5-year OS in patients are shown in **Figure 9**, and the calibration curves for predicting 1-, 3-, and 5-year CSS in patients are shown in **Figure 10**. The calibration curves for both training and validation sets are close to the

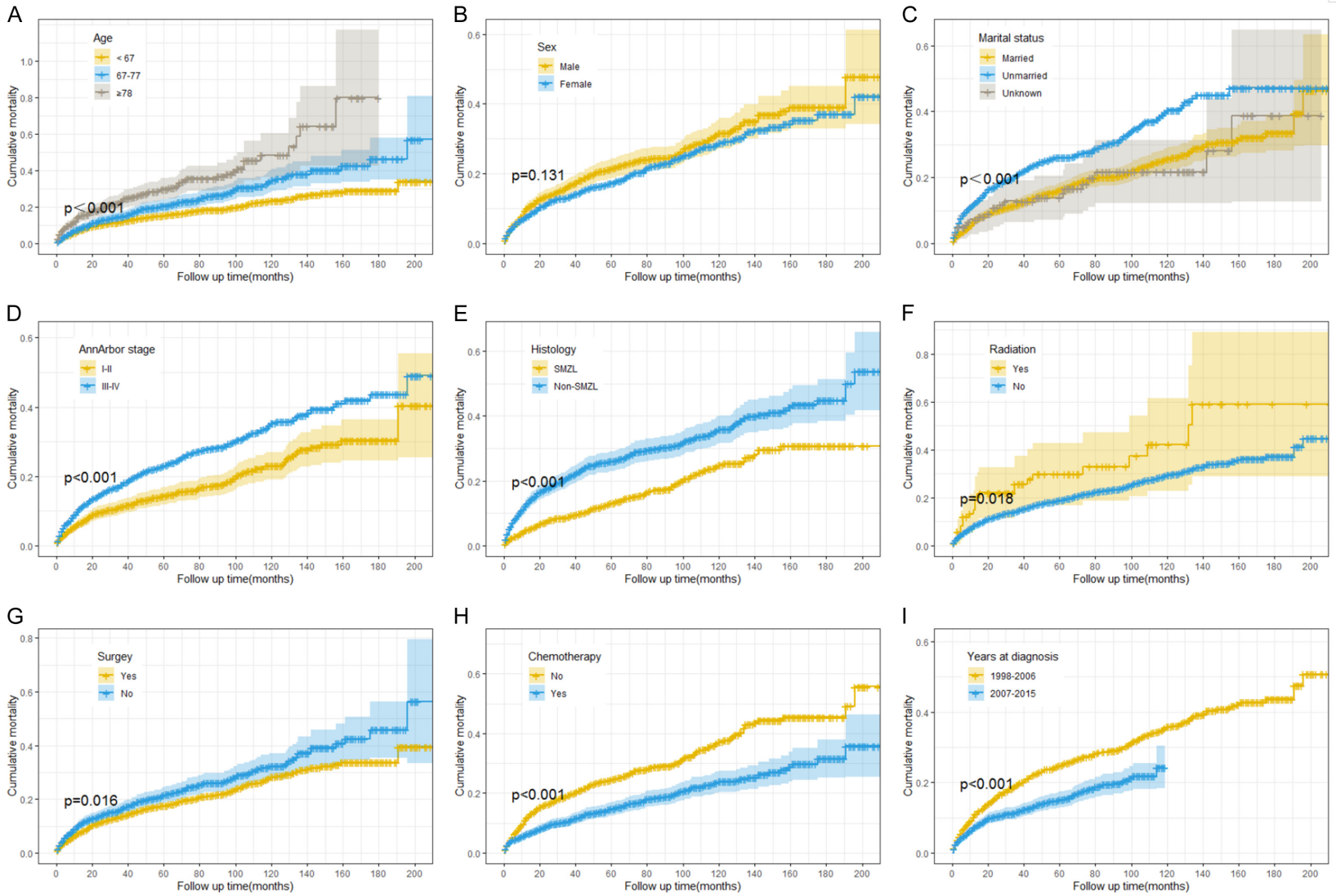

Figure 4. Cumulative cancer-specific mortality according to clinicopathological factors.

Table 5. Multivariate analysis of clinicopathological factors affecting cancer-specific survival in primary splenic lymphoma

Characteristic	HR	95% Confidence interval		*P* value
		Lower limit	Upper limit	
Age (years)				
<67	1			
67-77	1.381	1.135	1.137	0.001
≥78	2.189	1.755	2.731	<0.001
Marital status				
Married	1			
Unmarried	1.471	1.236	1.747	<0.001
Unknown	1.031	0.678	1.564	0.891
Ann Arbor stage				
III-IV:I-II	1.702	1.408	2.057	<0.001
Histology				
Non-SMZL:SMZL	1.793	1.478	2.176	<0.001
Radiotherapy				
No:Yes	0.791	0.529	1.181	0.251
Surgery				
No:Yes	1.056	0.881	1.268	0.557
Chemotherapy				
Yes:No	0.688	0.574	0.826	<0.001
Year at diagnosis				
2007-2015:1998-2006	0.678	0.565	0.813	<0.001

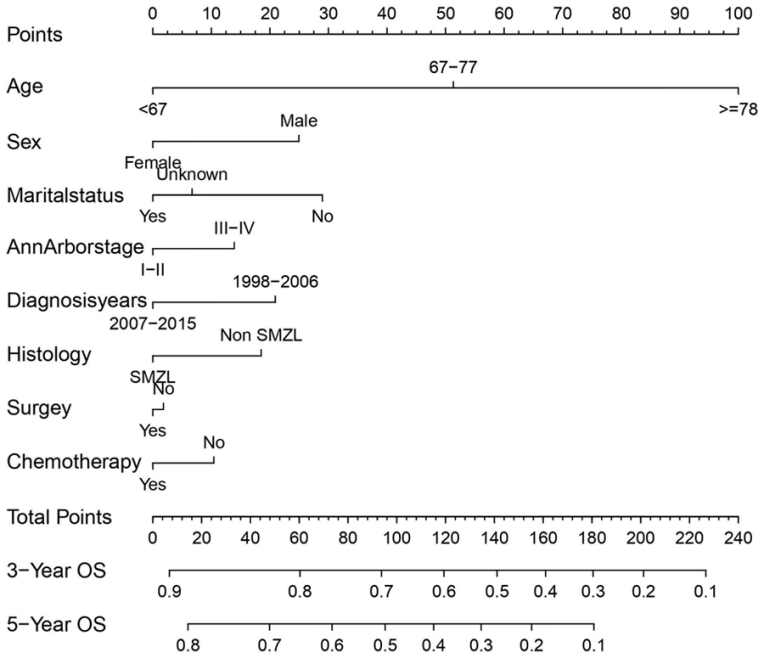

Figure 5. Nomogram for predicting overall survival (OS) in primary splenic lymphoma.

ideal 45° dashed line, indicating good consistency between predicted and actual observed values.

The DCA curves of nomogram predicting OS and CSS of PSL are shown in **Figure 11**. When the threshold probability of OS was in the range of 0.05-0.5, the net benefit level was significantly higher than that of "no intervention" and "full intervention", suggesting that the nomogram has good clinical applicability for predicting OS. In addition, when the threshold probability of CSS was between 0.2 and 0.6, the net benefit level was significantly higher than that of "no intervention" and "full intervention", suggesting that the nomogram has good clinical applicability for predicting CSS.

Web-based dynamic nomogram

Based on the above results, a dynamic nomogram for predicting OS (https://chenfandynnomogram.shinyapps.io/DynNomapp/) and CSS (https://chenfandynnomogram.shinyapps.io/DynNomapp-CSS/) in PSL patients was constructed. It builds on the previous nomogram to predict OS and CSS in patients. It is convenient and visualized, and can individually predict the survival rate of patients according to the clinical characteristics of patients. For example, a 78-year-old unmarried woman with SMZL histology and AnnArbor stage I-II was treated with surgery but not chemotherapy. Then her 5-year OS was predicated to be approximately 51.0% with a 95% CI of (0.440, 0.590). See **Figure 12**.

Discussion

The clinicopathological prognostic factors of PSL remain unclear. In this study, we analyzed the clinical features and survival outcomes of

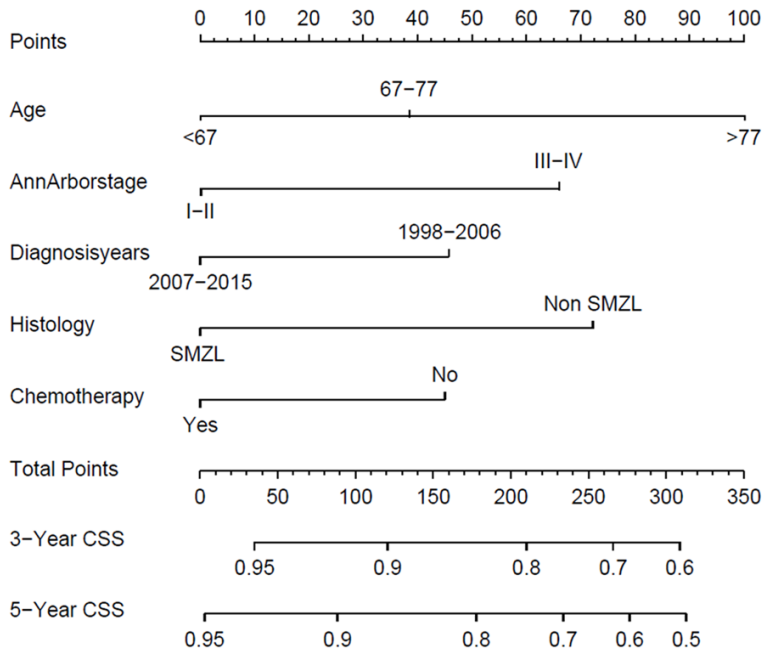

Figure 6. Nomogram for predicting cancer-specific survival (CSS) in primary splenic lymphoma.

PSL based on SEER database data, and then constructed a nomogram to predict patient survival and guide clinical decision-making. We also demonstrated the effect of conventional treatments such as surgery, chemotherapy, and radiotherapy on OS and CSS in PSL.

In this study, the clinical data of 4052 patients with PSL who met the research criteria were collected from the SEER database and randomly divided into a training set and an internal validation set. Multivariate Cox regression analysis on the training set showed that age, sex, marital status, AnnArbor stage, histology, surgery, chemotherapy and year at diagnosis were associated with the OS in PSL. Meanwhile, age, AnnArbor stage, histology, chemotherapy, and year at diagnosis were all independent prognostic factors for CSS in patients with PSL. Based these results, nomogram for predicting the 3- and 5-year OS and CSS was constructed. In addition, we also constructed a Web-based dynamic nomogram, accessible through the internet, enabling individualized assessment of the overall status of patients with PSL anytime and anywhere.

Age was proven to be an important prognostic factor for both OS and CSS in PSL. This study revealed that age over 67 years carry an increased risk. With the increase of age, the OS and CSS of patients decreased year by year. For patients over 78 years old, the 5-year OS was 47.1%, and the 5-year CSS was 74.2%. The prognosis of elderly patients is often poor, which may be related to their poorer constitution, more comorbidities and underlying diseases, intolerance to radiotherapy and chemotherapy, and poor tolerance to surgery.

Marital status was also found to be a prognostic factor for PSL. This study exhibited that unmarried patients had a worse prognosis than married patients. Being unmarried was a risk factor for both OS and CSS. Studies have shown that compared with married patients, unmarried patients, including widowed patients, have a significantly higher risk for metastatic cancer, undertreatment, and cancer-related death. This may be due to the fact that cancer can cause more distress than many other diseases. After being diagnosed with cancer, married patients showed less distress, depression, and anxiety than unmarried patients because their partners could share the emotional burden and provide appropriate social support [18]. This suggests that more psychological support and comfort should be provided in the clinical treatment for unmarried cancer patients.

Sex is also an independent influencing factor for the prognosis of PSL. This study revealed that compared with male patients, the prognosis of female patients was worse, showing as shorter OS. The data from GLOBOCAN 2020 show that there are 304,200 new non-Hodgkin lymphoma cases in males, ranking 10th, and 240,200 cases in females, ranking 12th. Worldwide, 147,200 males died from non-Hodgkin's lymphoma, ranking 10th; 112,500 females died, ranking 13th [19]. It can be seen that the morbidity and mortality of female patients with lymphoma are lower than those of male patients.

Table 6. C-index of the nomogram

Nomogram	Training set (95% CI)		Internal validation set (95% CI)		External validation set (95% CI)	
Nomogram on OS	0.678	(0.662, 0.694)	0.672	(0.648, 0.696)	0.704	(0.565, 0.843)
Nomogram on CSS	0.685	(0.661, 0.709)	0.683	(0.650, 0.716)	0.676	(0.488, 0.864)

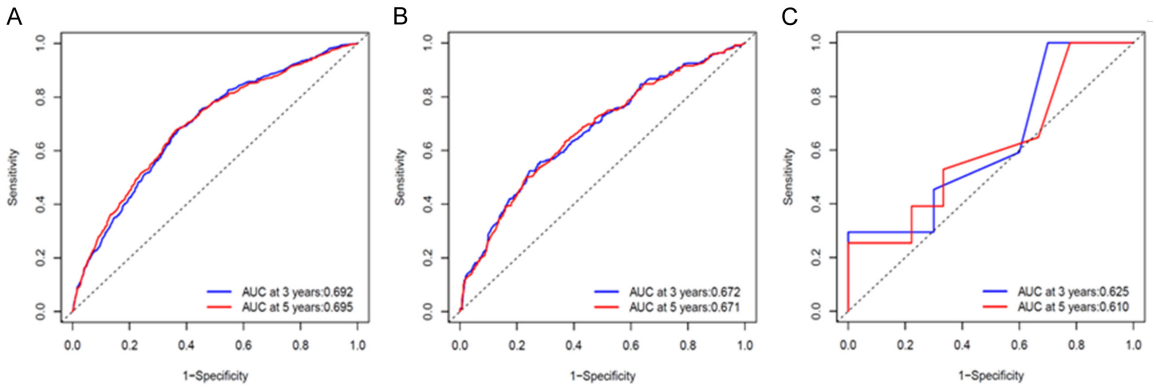

Figure 7. The ROC curves of nomogram predicting OS in primary splenic lymphoma. A. ROC curves of the 3-year and 5-year OS in the training set. B. ROC curves of the 3-year and 5-year OS in the internal validation set. C. ROC curves of the 3-year and 5-year OS in the external validation set. Abbreviations: ROC, receiver operating characteristic; OS, overall survival.

Table 7. Area under the ROC curve (AUC) of the nomogram

ROC curve	Training set			Internal validation set			External validation set		
	1-year	3-year	5-year	1-year	3-year	5-year	1-year	3-year	5-year
OS	0.732	0.692	0.695	0.705	0.672	0.671	0.632	0.625	0.610
CSS	0.714	0.699	0.677	0.693	0.691	0.652	0.638	0.646	0.589

OS: overall survival; CSS: cancer-specific survival.

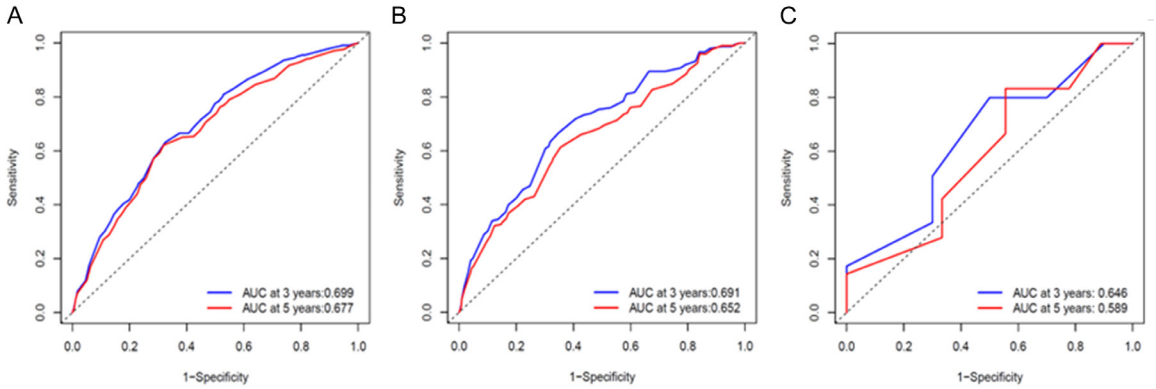

Figure 8. The ROC curves of nomogram predicting CSS in primary splenic lymphoma. A. ROC curves of the 3-year and 5-year CSS in the training set. B. ROC curves of the 3-year and 5-year CSS in the internal validation set. C. ROC curves of the 3-year and 5-year CSS in the external validation set. Abbreviations: ROC, receiver operating characteristic; CSS, cancer-specific survival.

The year at diagnosis was also an independent factor affecting the prognosis of PSL. This study showed that patients with PSL diagnosed between 2007 and 2015 had a better prognosis than those diagnosed between 1998 and 2006, showing as significantly longer OS and

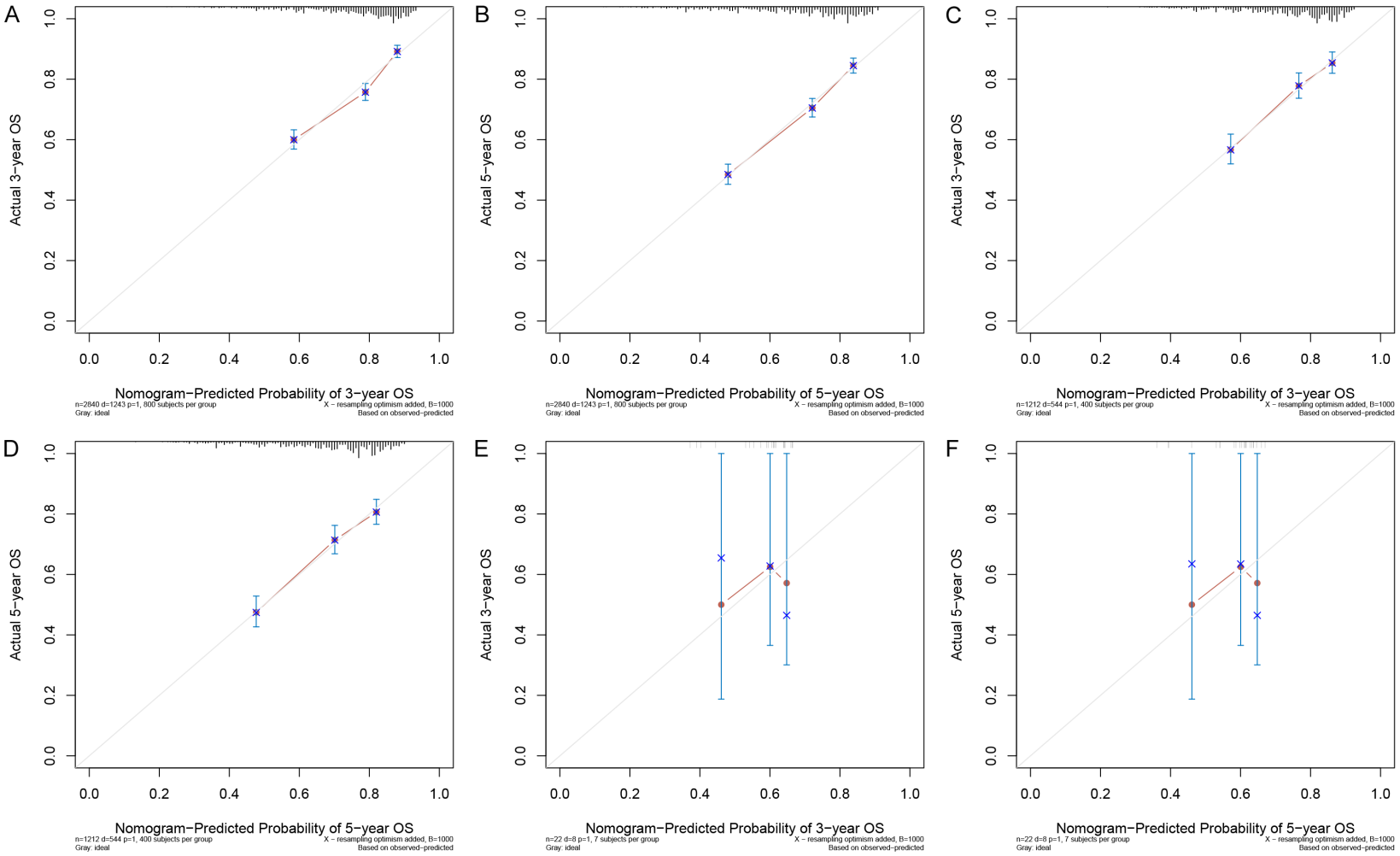

Figure 9. The calibration curves of nomogram predicting OS in primary splenic lymphoma. A, B. Calibration curves of the 3-year and 5-year OS in the training set. C, D. Calibration curves of the 3-year and 5-year OS in the internal validation set. E, F. Calibration curves of the 3-year and 5-year OS in the external validation set. Abbreviation: OS, overall survival.

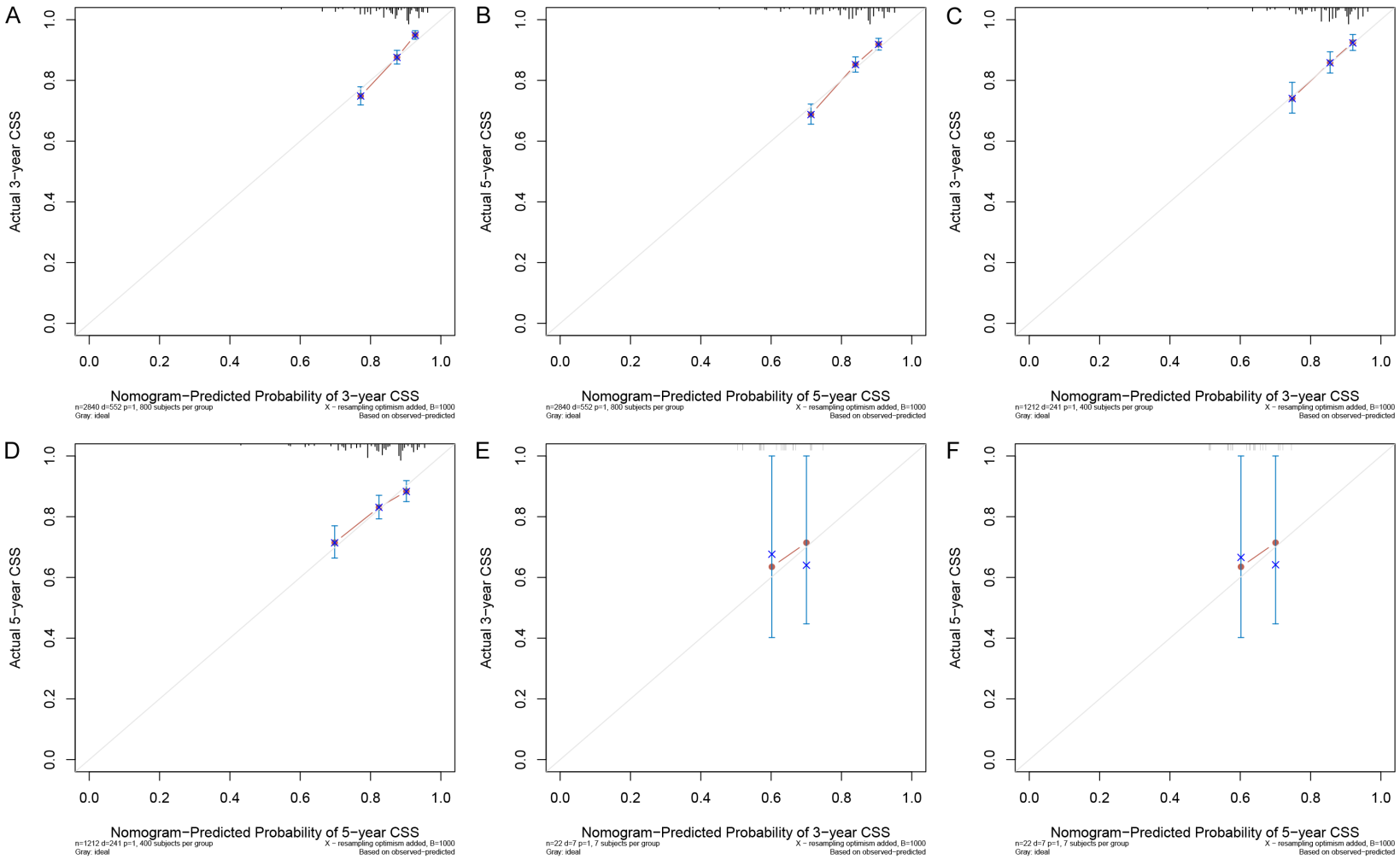

Figure 10. The calibration curves of nomogram predicting CSS in primary splenic lymphoma. A, B. Calibration curves of the 3-year and 5-year CSS in the training set. C, D. Calibration curves of the 3-year and 5-year CSS in the internal validation set. E, F. Calibration curves of the 3-year and 5-year CSS in the external validation set. Abbreviation: CSS, cancer-specific survival.

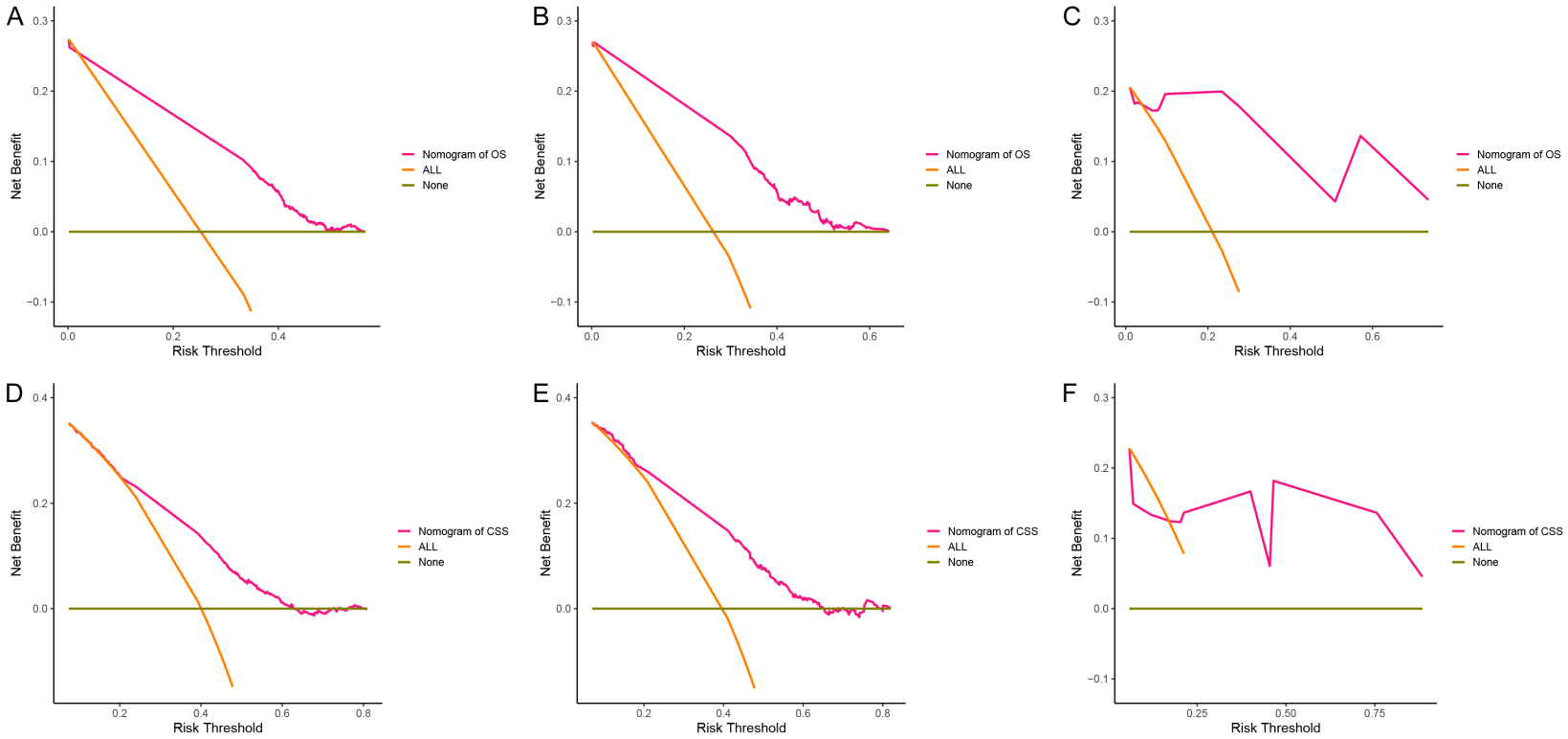

Figure 11. The DCA curves of nomogram predicting OS and CSS in primary splenic lymphoma. A-C. DCA curves of the OS in the training set, internal validation set and external validation set. D-F. DCA curves of the CSS in the training set, internal validation set and external validation set. Abbreviations: DCA, decision analysis curve; OS, overall survival; CSS, cancer-specific survival.

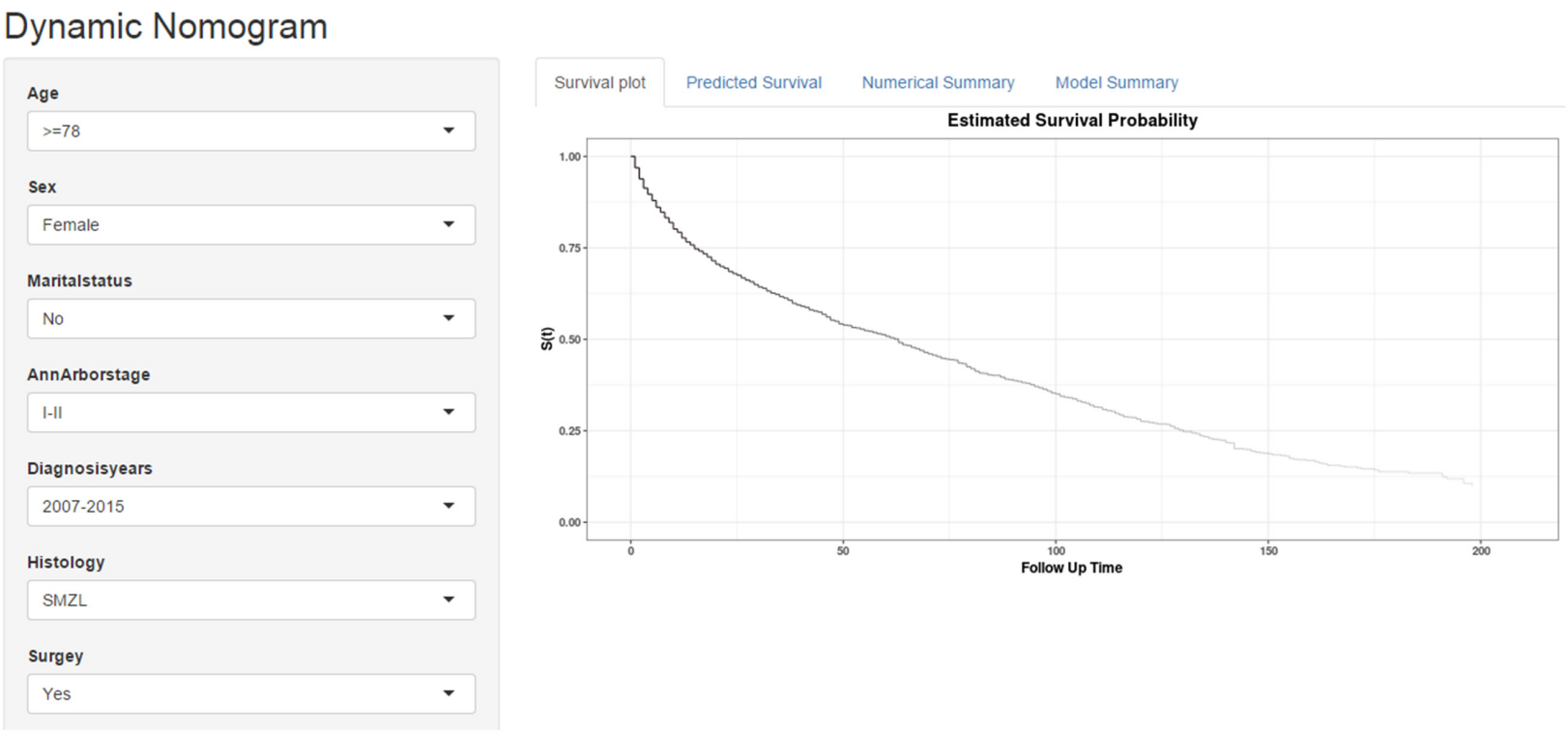

Figure 12. Web-based dynamic nomogram.

lower cumulative mortality. This may be related to the improvement of treatment methods, since the application of rituximab in the treatment of splenic lymphoma has effectively improved the survival of patients [20, 21].

The pathological types of PSL include SMZL, diffuse large B-cell lymphoma (DLBCL), and other subtypes such as follicular lymphoma [22]. SMZL is the most common histological subtype of PSL, accounting for 49% in our study. This contrasts with the results of a previous Japanese study of 115 patients, which showed that DLBCL was the most common subtype, followed by SMZL [23]. This difference may be due to the limited sample size of the previous study, which included only 115 patients, whereas our analysis included 4052 patients. The pathological type of disease was also a key factor affecting prognosis. This study showed that patients with SMZL had a better prognosis, namely longer OS and CSS, than patients with other pathological types, which is consistent with previous studies. In addition, it has been reported that patients with DLBCL tend to be older, have higher levels of LDH, and are more likely to develop tumors compared to those with SMZL [24].

Disease stage was another independent prognostic factor. Patients with advanced stages are more likely to have a poor prognosis. Ahmann et al. divided PSL into three stages: stage I refers to disease confined to the spleen; stage II refers to involvement of the spleen and hilar lymph nodes; and stage III refers to extrasplenic lymph nodes or liver involvement [25]. Due to the limitations of database, this study used the AnnArbor staging to divide the disease into four stages. The results showed that patients with stage III-IV had a worse prognosis compared with stage I-II patients.

Splenectomy remains an effective method of diagnosis and treatment [26]. This study found that surgery was a prognostic factor for PSL. Compared with surgical patients, non-operated patients had a worse prognosis, with significantly shorter OS. A previous small sample study reported that patients with PSL had a good prognosis after splenectomy [27]. The study by Sachin et al. showed that splenectomy could prevent the occurrence of potential complications due to hypersplenism and rupture of the spleen. The study by Kraus et al. also suggested that splenectomy is not only a treatment, but also an important diagnostic method for PSL [28]. However, splenectomy is associated with both short-term and long-term complications. The exact incidence of splenectomy-related complications in patients with SMZL is unknown, as this information has not been provided in many reports. Therefore, decisions regarding splenectomy should be made with caution, especially in patients with multiple significant complications. Splenectomy may be considered for patients eligible for surgery who exhibit symptomatic splenomegaly, mild to moderate bone marrow infiltration, and an absence of large lymphadenopathy.

Receiving chemotherapy was found to be an important protective factor in PSL (longer OS and CSS). A study of 50 patients with SMZL by Cervetti showed that the addition of rituximab to 2-CdA (a purine analog) significantly improved the rate of complete remission and prolonged the duration of remission [29]. Therefore, rituximab combined with chemotherapy can significantly improve the prognosis of patients with PSL, and immunochemotherapy can be used in cases where splenectomy cannot be performed. However, it is unclear which chemotherapy regimens are most effective when used in combination with rituximab.

In addition, the results of this study showed that there was no significant difference in the OS and CSS between patients with or without radiotherapy. Therefore, radiotherapy should be carefully selected when formulating a treatment plan.

Based on large sample data, this study explored the clinical characteristics of PSL and constructed the nomogram to predict the survival, which provided a reference for the formulation of clinical guidelines. The internal validation results showed that the nomogram model has not only a good predictive value, but also a good clinical applicability. In addition, the predictive models constructed in this study were validated with external data, which makes our results more generalizable than those of small cohort or case review studies.

However, this study still has some limitations. First, the data are from the SEER database,

which inherently carries biases in retrospective analysis that are difficult to eliminate, so the constructed nomogram needs to be validated in large-scale prospective studies. Second, the SEER database does not provide molecular pathological information of cases, such as the expression of MIB-1 and BCL2, and the included prognostic factors can also be adjusted. Third, the SEER database lacks laboratory findings, which could reveal abnormal blood counts, such as neutropenia, hemoglobin levels, thrombocytopenia, or lymphocytosis. Elevated levels of lactate dehydrogenase have also been seen in patients with splenic lymphoma, which is also associated with poorer prognosis. Forth, there are no detailed chemotherapy regimens in the SEER database, so it is impossible to evaluate appropriate treatment regimens. Fifth, due to the limited number of patients in the SEER database and the small number of patients undergoing radiotherapy, the effect of radiotherapy on prognosis may not be reliable. Finally, although the nomogram showed good discrimination and validation, it's worth noting that the values of C-index and AUC were not particularly high.

Conclusion

The nomogram model constructed in this study for predicting the survival prognosis of patients with PSL has good predictive value. This tool can offer clinicians a more accurate and practical means of individualized, rapid, and accurate prediction of the survival prognosis of patients.

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Written informed consent was obtained from patients.

Disclosure of conflict of interest

None.

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