

Epidemiologic Characteristics, Prognostic Factors and Treatment Outcomes in Primary Central Nervous System Lymphoma: A SEER-Based Study

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Abstract

Objective: To study the clinical characteristics, prognostic factors and treatment outcomes in patients with primary central nervous system lymphoma (PCNSL).

Materials and Methods: The data of total 5166 PCNSL patients diagnosed between 2000 and 2018 from the Surveillance, Epidemiology, and End Results (SEER) database was obtained.

Results: The mean age was 63.1 ± 14.9 years, with a male to female of 1.1:1.0. The most common histologic subtype was diffuse large B-cell lymphoma (DLBCL) (84.6%). The 1-, 3-, and 5-year OS were 50.1, 36.0 and 27.2% and corresponding to DSS were 54.4, 41.3 and 33.5%, respectively. Multivariate analysis with Cox regression showed that race, sex, age, marital status, surgery, chemotherapy and radiotherapy were independent prognostic factors for OS, but radiotherapy no longer for DSS. Nomograms specially for DLBCL were established to predict the possibility of OS and DSS. The concordance index (C-index) of OS and DSS were 0.704 (95% CI 0.687-0.721) and 0.698 (95% CI 0.679-0.717), suggesting the high discrimination ability of the nomograms.

Conclusion: Surgery or/and chemotherapy was favourably associated with better OS and DSS. However, radiotherapy did not benefit to OS and DSS in the long-term. A new predictive nomogram and a web-based survival rate calculator we developed showed favorable applicability and accuracy to predict the long-term OS for DLBCL patients specifically.

Introduction

Primary central nervous system lymphoma (PCNSL) is an uncommon and highly invasive tumor that involve the leptomeninges, brain, eyes or spinal cord without evidence of systemic disease[1]. PCNSL accounts for 1%-2% of non-Hodgkin lymphoma (NHL) and the most (over 90%) cases are DLBCL[2, 3]. Immunocompromised individuals, such as HIV-infected or immunosuppressive patients, are deemed to have a higher risk in PCNSL[4, 5]. PCNSL was historically associated with poor prognosis, with an overall survival (OS) of 1.5 months without additional treatment. The high-dose methotrexate (HD-MTX) systemic chemotherapy is deemed as the standard first-line treatment, however, few patients can achieve long-term survival, the median progression-free survival (PFS) and OS were only 24.0, and 36.9 months respectively[6, 7], and the 5-year OS in the period 1992-1994 was increased only from 19.1–30.1% in the period 2004-2006[4]. Surgery is generally discouraged previously before 2010, but conventional view has been challenged as the advances in surgical techniques. Due to the high risk of neurotoxicity and lacking of sustainable response, PCNSL patients should avoid whole brain radiation (WBRT) in the first-line treatment, more research has focused on whether different radiotherapy regimens (including reduced-dose and partial-brain radiotherapy) combination chemotherapy can bring benefits. However, the conclusions are inconsistent. In recent years, novel agents including immune checkpoint inhibitors, immunomodulatory drugs (IMiDs), bruton tyrosine kinase (BTK) inhibitor, PI3K/AKT/mTOR inhibitors and chimeric antigen receptor T cell (CAR-T cell) therapy have been applied in several clinic trials which

exhibit promising clinic outcomes. Even with an impressive clinical response, more randomized clinical trials are still needed to verify and identify the optimal therapy for PCNSL patients.

Two prognostic classification systems of PCNSL are widely used currently. The IELSG identified an age (>60 years), elevated lactate dehydrogenase (LDH) serum level, performance status (PS) (≥ 2), high CSF protein concentration, and extensive deep structure involved in the brain were independent predictors of negative prognosis[8]. In another prognostic model, the MSKCC prognostic score described three risk groups based on age and Karnofsky performance status (KPS)[9]. However, treatment information was not included in these prognostic systems, it is difficult to perform the treatment choose based on these prognostic systems. Therefore, a new, easily available prognostic system which include treatment information is needed to be developed.

Duing to the rarity of PCNSL, large-scale clinical trials and prospective data are limited for us to investigate it. The Surveillance, Epidemiology, and End Results (SEER) contains a wealth of relevant information on different types of cancer patients based on the United States population which provides excellect resources for us to study. Therefore, a large population-based analysis was conducted to describe the clinical characteristics, prognostic factors and treatment outcomes of PCNSL using the SEER database. We also analyzed independent prognostic factors of PCNSL and established a nomogram to predict the prognosis in this population.

Materials And Methods

Study data was obtained using the SEER*Stat software (version 8.3.9). By “Incidence-SEER Research Plus Data, 18 Registires, Nov 2020 Sub (2000-2018)”, patients diagnosed with PCNSL between 2000 and 2018 were identified. International Classification of Diseases for Oncology (ICD-O-3) histologic codes (9590–9595, 9650–9699, 9702–9729) were used for lymphoma and primary sites limited to central nervous system were identified by site specific code (C71.0–C71.9). Unknown age of diagnosis, uncertain race, unknown sex, unknown marriage status, incomplete follow-up data and secondary to other tumors were excluded. The primary endpoint of this study were overall survival (OS) and disease-specific survival (DSS).

Statistical Analyses

The OS and DSS were estimated with the Kaplan-Meier method using the log-rank test, and Cox regression model was used for univariate and multivariate survival analysis. Nomograms were constructed to predict 1-, 3-, and 5-year OS and DSS specifically for DLBCL according to the results of multivariable Cox regression analysis. To evaluate the accuracy of the nomograms, Harrell's concordance index (C-index) was calculated to quantify the discrimination performance and calibration curve was plotted to identify whether the predicted survival was consistent with the actual survival. The data were analyzed using R software (R version 4.0.4). Statistical significance was set at $P < 0.05$ (two-sided).

Results

Epidemiologic Characteristics of PCNSL Patients

The mean age at diagnosis was 63.1 ± 14.9 , ranging from 3 to 97 years. The population was comprised of 2679 (51.9%) males and 2487 (48.1%) females, and the highest incidence of age group was 70-79 years old. The characteristics of PCNSL patients were summarized in TABLE 1.

Regarding the clinical aggressiveness and cell line of origin, there were 4429 (85.7%) patients of aggressive B cell NHLs, 166 (3.2%) indolent B cell NHLs, 474 (9.2%) NHL-NOSs and 85 (1.6%) T cell NHLs. As for the histological classification of PCNSL, the most common subtype was DLBCL (84.6%), followed by not otherwise specified (NHL-NOS) (9.2%), follicular lymphoma (FL) (1.3%), peripheral T-cell lymphoma (PTCL) (1.2%), mucosal-associated lymphoid tissue (MALT) (1.2%), burkitt's lymphoma (BL) (0.7%), lymphoplasmacytic lymphoma (LPL) (0.4%), anaplastic large cell lymphoma (ALCL) (0.4%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (0.4%). Except for ALCL (median age 39.0), the median age of all subtypes were over 60 years old. The epidemiologic characteristics and survival outcomes were summarized according to histological subtype in TABLE 2.

Survival Analysis

A total of 3660 patients died during the follow-up period, 3101 deaths were disease-specific. Kaplan-Meier curves illustrating OS and DSS were shown in Figures 1A, B. The median OS and DSS was 13.0 and 19.0 months. The 1-, 3-, and 5-year OS were 50.1, 36.0 and 27.2% and corresponding to DSS were 54.4, 41.3 and 33.5%, respectively. Patients diagnosed in 2009 to 2018 showed better OS and DSS than patients diagnosed in 2000 to 2008 ($P < 0.0001$) (Figures 1C, D).

In the whole cohort, the best 3-year OS and DSS were observed in MALT (OS: 78.3%, DSS: 86.0%) and FL (OS: 53.8%, DSS: 57.4%). In addition, the Kaplan-Meier survival curves for OS and DSS of the main histological subtypes were presented in Figures 1E, F. Furthermore, Kaplan-Meier survival analysis was also performed stratifying patients according to sex, age, race, marital status and treatment. It was found that increasing age was significantly associated with reduced OS and DSS (Figures 2A, E). Females had significantly better OS and DSS than males (Figures 2B, F). We also found that patients who were others (Figures 2C, G) and married (Figures 2D, H) had a better OS and DSS according to the univariate analysis.

In terms of treatment, patients who underwent chemotherapy (Figures 3A, D) or surgery (Figures 3C, F) achieved significantly longer OS and DSS than who did not. However, radiotherapy led to worse OS and DSS in the long-term (Figures 3B, E). We also explored the outcome in combination therapy and found that surgery combined with chemotherapy was associated with better OS and DSS (Figures 4A, B), but radiotherapy combined with chemotherapy led to worse OS and DSS in the long-term (Figures 4C, D). Then, we performed multivariate Cox-regression analysis to figure out the independent prognostic factors for OS and DSS and revealed race, sex, age, marital status, surgery, chemotherapy and radiotherapy were

independent predictors of OS, but radiotherapy was no longer an independent prognostic factor for DSS (Table 3).

Construction of Nomogram

Considering the main histological subtype of PCNSL was DLBCL, we developed a prediction model specifically for DLBCL patients. 4373 patients with DLBCL were randomly divided into a training cohort (n=3061) and a validation cohort (n=1312) in a ratio of 7:3 for model construction and validation. Firstly, univariate and multivariate Cox regression analyses were conducted to select the independent prognostic factors for OS and DSS. Univariate and multivariate analyses results were displayed in Table 4. These significant factors from univariate Cox regression analysis were incorporated into multivariate analysis. Significant predictors of OS and DSS on multivariate analysis were used to establish the nomograms. The OS and DSS nomogram at the 1-, 3-, and 5- year were shown in Figure 5. Then, the nomogram performance was assessed with discrimination and calibration by using the external validation cohort. The C-index of OS and DSS were 0.704 (95% CI 0.687-0.721) and 0.698 (95% CI 0.679-0.717), indicating the high discrimination ability of the nomograms. The calibration curves of the train cohort and the external validation cohort were presented in Figure 6, which represented good agreement among the predicted survival and the actual survival at 1-, 3-, and 5-year.

Web-Based Survival Rate Calculator

A dynamic web-based survival rate calculator base on the nomogram was established to predict the long-term OS (<https://tangdongshengarticle.shinyapps.io/DynNomapp/>). For instance, a 75-year-old white married man was diagnosed as PCNSL with DLBCL, if he refused surgery and chemotherapy, his 3-year OS rate is approximately only 4.6% (95% CI 0.022-0.101), if he was given surgery and chemotherapy, his 3-year OS rate is approximately 34.0% (95% CI 0.272-0.420) (Figure 7).

Discussion

PCNSL represents a rare but highly aggressive NHL with poor prognosis. In light of the rarity of PCNSL, current understanding of PCNSL is mainly based on retrospective analysis with small series. Therefore, we conducted a study based on a large population. In the current study, there were 5166 PCNSL patients from SEER database.

The mean age at diagnosis was 63.1 ± 14.9 years, and the male to female ratio was 1.1:1.0, which was largely consisting with population-based study from Australia[10]. Previous studies have demonstrated that age was a significant and adverse prognostic factor[11–13]. In the present study, inferior OS and DSS were significantly associated with older age, consisting with previous results. Interestingly, our study revealed that married patients tend to have better outcomes than single patients (including divorced/widowed/separated patients). The mechanism between marital status and survival is unclear, social-psychological factors may contribute to it. The married patients may have better socioeconomic status and more emotional support than single patients.

Although the introduction of HD-MTX has significantly improved PCNSL prognosis, numerous patients still die attributed to treatment-related mortality, chemotherapy-resistant disease and relapse[14]. Recent progress in understanding the pathophysiology of PCNSL has led to novel therapeutics introduced into clinical trials and have shown promising clinical responses[15]. Based on population analysis, we found that patients diagnosed between 2009-2018 had better OS and DSS than those diagnosed 2000-2008, which reflected developments in treatment.

PCNSL is characterized by a frequent early wide dissemination and the involvement of deep brain that leads to poor efficacy of surgery[16]. Previous research suggested that surgical resection (including complete and partial surgical resection) have no significant survival advantage and even be associated with higher mortality that should be avoided[17, 18]. The role of surgery is to only establish a diagnosis by stereotactic biopsy. However, with the large number of applications of new techniques and practices in recent years, including increased use of MRI, frameless stereotyping and tumor visualization, the effectiveness and tolerability have greatly improved. Survival advantage was proven and the traditional view has been questioned in some studies[19–21]. Therefore, the role of surgery in PCNSL should be reevaluated. In our study, surgical excision was associated with significantly better OS and DSS, and was an independent risk factor for survival. Moreover, combining surgical excision and chemotherapy can bring favourable OS and DSS than chemotherapy alone, which suggested that multimodal therapy may be more beneficial. However, this results should be interpreted with caution because of unknown operation mode and variations in the technical level of operators, and more prospective research is needed to verify it.

Due to the high sensitivity to radiation, newly diagnosed patients with PCNSL have historically received whole-brain radiotherapy (WBRT). However, WBRT-associated delayed neurotoxicity has limited its use, especially for age older than 60 years[7, 22, 23]. Given the higher risk of neurotoxicity and the limited durability of treatment responses, WBRT is not considered as the standard initial therapy for PCNSL patients[24, 25]. Recently, many clinical studies have engaged in whether different radiotherapy regimens (including reduced-dose and partial-brain radiotherapy) combination with chemotherapy can bring better clinical outcomes[26–30]. However, the results still remain controversial. Analysis based on a large population, radiotherapy did not improve long-term effects and associated with inferior OS and DSS compared with no radiotherapy according to univariate analysis. Multivariate analysis revealed radiotherapy was an independent prognostic factor for OS, but not for DSS. We further explored the combination of radiotherapy and chemotherapy, then found that patient may benefit from combination therapy in the early stage of the treatment, unfortunately, the long-term outcomes were not superior to chemotherapy alone because of the high incidence of delayed neurotoxicity and short-term responses. Giving above, the benefit of radiotherapy in establishing local control of tumors must be weighed against the increased risk of long-term neurotoxicity. Due to unknown information about detailed radiotherapy and chemotherapy regimens, subgroup analysis could not be performed. Therefore, these results should be interpreted cautiously.

The nomogram has become a useful tool for clinical decision-making and visualized and quick risk assessment for clinicians. In this study, it was found that race, age, sex, marital status, chemotherapy and surgery were independent prognostic factors for OS and DSS in DLBCL patients, and we constructed the nomograms to predict 1-, 3-, and 5-year survival based on these factors. The significantly higher C-index 0.704 and 0.698 of the nomograms proved discriminative power. Moreover, the calibration curve exhibited good consistency among the predicted survival and the actual survival. However, due to manual calculations, the nomograms are not easy to apply to clinical practice, so we further developed a dynamic web-based survival rate calculator that can predict the long-term OS dynamically at different time points for DLBCL patients based on the nomogram (<https://tangdongshengarticle.shinyapps.io/DynNomapp/>).

This study has several limitations. Firstly, potential biases were unavoidable as a retrospective study. Secondly, other potential prognostic factors, such as Karnofsky performance status score, size and number of lesions, LDH level are not registered in SEER database, and cannot combine these factors to predict prognosis. Thirdly, detail chemotherapy, surgical operation mode and radiotherapy regimens for patients are not available. We are unable to further analyze the impact of different treatment regimen on prognosis. Lastly, the nomograms were established and verified by using the same database, so it is necessary to prospectively verify the nomogram in another independent data set for reliable evaluation. Therefore, the results of the present study should be interpreted with caution given above limitations. Whereas, our study still provided useful information and important insights in PCNSL despite these limitations based on a large population.

In conclusion, age, race, sex, use of chemotherapy, surgery and radiation were independent prognostic factors for OS, but radiotherapy was no longer an independent prognostic factor for DSS based on the SEER database. Surgery might be a therapeutic benefit for PCNSL patients. Radiotherapy was effective in therapeutic initial stage, but the long-term outcome was not satisfactory. We also developed a predictive nomogram and a web-based survival rate calculator predicting the long-term OS in DLBCL patients which showed favorable applicability and accuracy that could help in the prediction of mortality and the choice of treatment.

Declarations

Ethics statement

Not applicable.

Data availability statement

The data from this study are available in the SEER database, <https://seer.cancer.gov>.

Conflicts of Interest

The authors declared that they have no competing interests.

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Tables

TABLE 1 | Patient and tumor characteristics of primary central nervous system lymphoma diagnosed in SEER 18 registries, 2000-2018.

Characteristic	No. of patients	Percentage (%)
total	5166	100
Age at diagnosis, years		
Mean±SD	63.1±14.9	
Median(rang)	65.0(3.0-97.0)	
Sex		
Male	2679	51.9
Female	2487	48.1
Race		
White	4182	81.0
Black	364	7.0
Others ^a	620	12.0
Years of diagnosis		
2000-2008	2115	40.9
2009-2018	3051	59.1
Age		
<50	916	17.7
50-59	884	17.1
60-69	1372	26.6
70-79	1415	27.4
≥80	579	11.2
Marital status		
Married	3045	58.9
Single ^b	2121	41.1
Lineage		
Aggressive B cell NHL ^c	4429	85.7
Indolent B cell NHL ^d	166	3.2
T cell NHL	85	1.6
NHL-NOS	474	9.2

Others	12	0.2
<hr/>		
Surgery		
<hr/>		
No	3040	58.8
<hr/>		
Performed	2126	41.2
<hr/>		
Radiation		
<hr/>		
No	3608	69.8
<hr/>		
Performed	1558	30.2
<hr/>		
Chemotherapy		
<hr/>		
No/unknown	1652	32.0
<hr/>		
Performed	3514	68.0
<hr/>		

NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

^aAmerican Indian/Alaskan Native or Asian/Pacific Islander.

^bIncluded divorced/separated/widowed patients.

^cIncluded diffuse large B cell lymphoma, burkitt's lymphoma, mantle cell lymphoma, and intravascular large B-cell lymphoma.

^dIncluded follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and mucosa associated lymphoid tissue lymphoma.

TABLE 2 | Patient characteristics according to the histological subtypes

Histology subtype	n(%)	Median age	Male(%)	Survival			
				Median OS,m	3-year OS	Median DSS,m	3-year DSS
All patient	5166						
DLBCL	4373(84.6)	66.0	51.8	12	35.3	17	40.5
NHL-NOS	474(9.2)	65.0	54.0	8	32.0	11	37.3
FL	65(1.3)	67.0	41.5	58	53.8	77	57.4
PTCL	63(1.2)	60.0	57.1	15	37.9	26	47.3
MALT	60(1.2)	60.0	31.7	/	78.3	/	86.0
BL	34(0.7)	60.0	64.7	19	38.3	19	42.3
LPL	22(0.4)	63.0	45.5	/	50.9	/	50.9
ALCL	21(0.4)	39.0	71.4	13	34.4	22	37.2
CLL/SLL	19(0.4)	66.0	47.4	29	42.1	47	54.0
Others	35(0.7)	62.0	54.3	/	/	/	/

n, number of cases; m, month; OS, overall survival; DSS, disease-specific survival; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma, BL, Burkitt's lymphoma; CLL/SLL, Chronic lymphocytic leukemia/small lymphocytic lymphoma; MALT, Mucosal-associated lymphoid tissue. PTCL, Peripheral T-cell lymphoma, ALCL, Anaplastic large cell lymphoma. LPL, Lymphoplasmacytic lymphoma.

TABLE 3 |Multivariable Cox regression analysis of the independent prognostic factors for OS and DSS among PCNSL patients.

Variables	Overall survival			Disease-specific survival		
	HR	95% CI	P	HR	95% CI	P
Race						
White	Reference			Reference		
Black	1.21	1.06-1.39	0.005	1.25	1.08-1.44	0.003
Others	0.92	0.83-1.03	0.138	0.91	0.81-1.02	0.094
Sex						
Male	Reference			Reference		
Female	0.84	0.78-0.89	<0.001	0.86	0.80-0.93	<0.001
Age						
<50	Reference			Reference		
50-59	1.48	1.31-1.67	<0.001	1.32	1.16-1.50	<0.001
60-69	1.90	1.70-2.13	<0.001	1.69	1.50-1.90	<0.001
70-79	2.65	2.37-2.96	<0.001	2.28	2.03-2.56	<0.001
≥80	3.32	2.91-3.79	<0.001	2.76	2.39-3.19	<0.001
Years of diagnosis						
2000-2008	Reference			Reference		
2009-2018	0.79	0.74-0.84	<0.001	0.77	0.72-0.83	<0.001
Marital status						
Married	Reference			Reference		
Single	1.21	1.13-1.30	<0.001	1.22	1.13-1.31	<0.001
Classification						
Aggressive B cell NHL	Reference			Reference		
Indolent B cell NHL	0.33	0.27-0.42	<0.001	0.31	0.24-0.40	<0.001
T cell NHL	0.82	0.63-1.07	0.148	0.80	0.59-1.07	0.132
NHL-NOS	0.96	0.86-1.08	0.501	0.95	0.85-1.07	0.432
Others	1.08	0.52-2.28	0.834	1.09	0.49-2.43	0.838
Surgery						
Performed	Reference			Reference		

No/unknown	1.34	1.25-1.43	<0.001	1.36	1.26-1.46	<0.001
Chemotherapy						
Performed	Reference			Reference		
No/unknown	2.73	2.53-2.94	<0.001	2.59	2.39-2.81	<0.001
Radiation						
Performed	Reference			Reference		
No/unknown	1.12	1.04-1.20	0.003	1.08	1.00-1.17	0.054

TABLE 4 | Univariate and multivariate Cox regression analysis of each factor's ability in predicting OS and DSS among DLBCL patients.

	Overall Survival			Disease-Specific Survival		
	HR	95% CI	P	HR	95% CI	P
UNIVARIATE ANALYSES						
Race						
White vs Black	1.16	1.00-1.34	0.046	1.21	1.04-1.42	0.014
White vs Others	0.85	0.76-0.95	0.004	0.83	0.73-0.94	0.003
Sex						
Male vs Female	0.92	0.86-0.99	0.021	0.93	0.86-1.00	0.054
Age						
0-50 vs 50-59	1.05	0.92-1.20	0.453	0.94	0.82-1.07	0.342
0-50 vs 60-69	1.39	1.23-1.55	<0.001	1.22	1.08-1.38	0.001
0-50 vs 70-79	2.19	1.96-2.45	<0.001	1.89	1.68-2.13	<0.001
0-50 vs ≥80	3.25	2.83-3.73	<0.001	2.73	2.35-3.16	<0.001
Marital status						
Married vs Single	1.23	1.14-1.32	<0.001	1.27	1.18-1.37	<0.001
Surgery						
Performed vs No/unknown	1.27	1.18-1.37	<0.001	1.30	1.21-1.41	<0.001
Chemotherapy						
Performed vs No/unknown	3.17	2.95-3.41	<0.001	3.03	2.80-3.28	<0.001
Radiation						
Performed vs No/unknown	0.83	0.77-0.89	<0.001	0.80	0.74-0.87	<0.001
MULTIVARIATE ANALYSES						
Race						
White vs Black	1.17	1.01-1.36	0.042	1.18	1.00-1.39	0.048
White vs Others	0.88	0.79-0.99	0.028	0.86	0.76-0.97	0.017

Sex						
Male vs Female	0.84	0.78-0.90	<0.001	0.86	0.79-0.93	<0.001
Age						
0-50 vs 50-59	1.35	1.18-1.54	<0.001	1.20	1.04-1.38	0.013
0-50 vs 60-69	1.74	1.54-1.96	<0.001	1.53	1.35-1.74	<0.001
0-50 vs 70-79	2.43	2.16-2.74	<0.001	2.10	1.85-2.38	<0.001
0-50 vs ≥80	3.03	2.63-3.50	<0.001	2.55	2.18-2.97	<0.001
Marital status						
Married vs	1.21	1.12-1.31	<0.001	1.23	1.13-1.33	<0.001
Single						
Surgery						
Performed vs	1.32	1.22-1.42	<0.001	1.34	1.24-1.45	<0.001
No/unknown						
Chemotherapy						
Performed vs	2.97	2.74-3.22	<0.001	2.80	2.56-3.05	<0.001
No/unknown						
Radiation						
Performed vs	1.08	1.00-1.17	0.053	1.04	0.95-1.13	0.394
No/unknown						

Figures

Figure 1

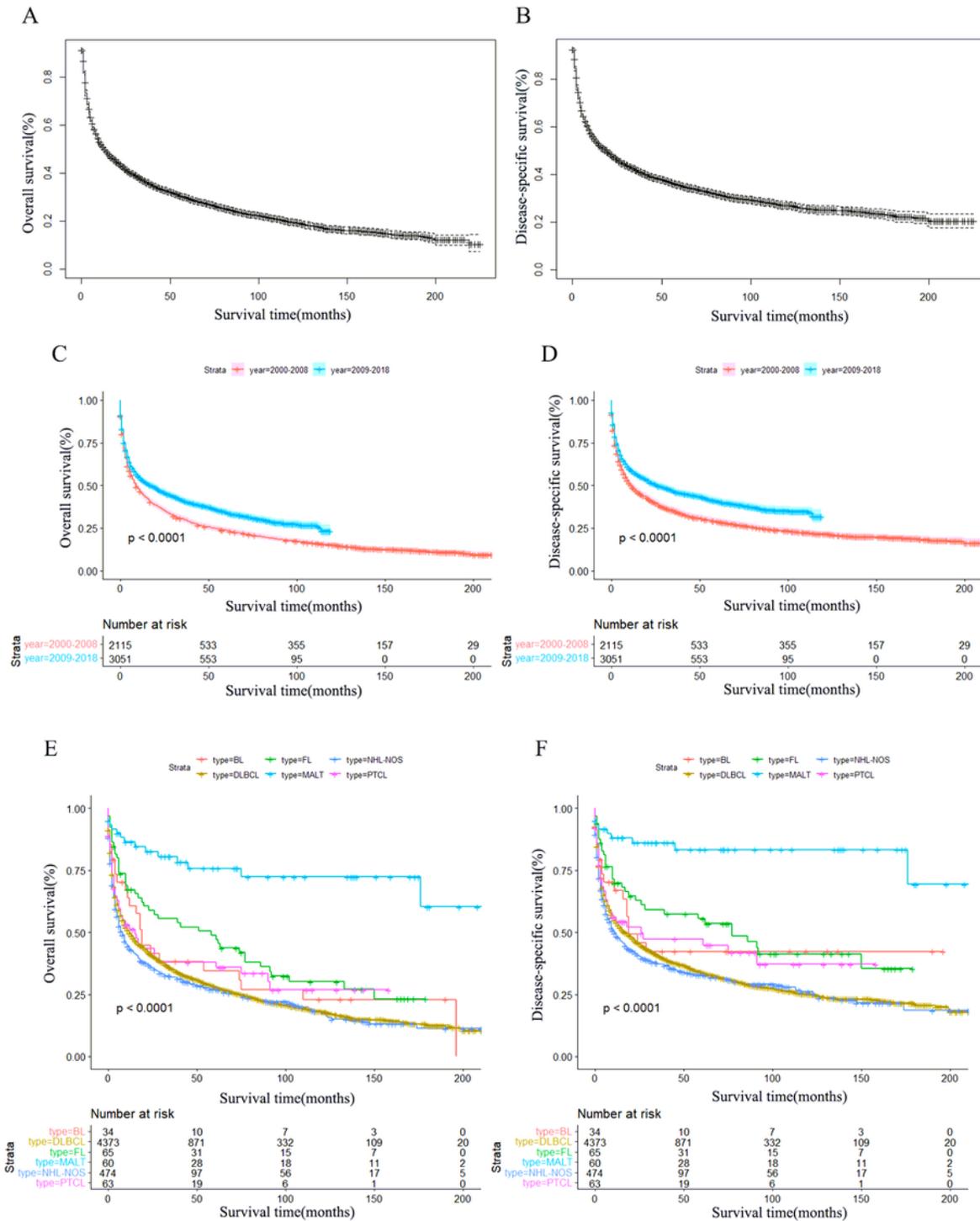


Figure 1

Survival analysis of primary central nervous system lymphoma. OS (A) and DSS (B) curves for all patients. Survival analysis according to the year of diagnosis, OS (C) and DSS (D) have significantly improved in the past decades, $P < 0.0001$. Survival curves of OS (E) and DSS (F) according to the main histological subtypes. MALT, Mucosal-associated lymphoid tissue; DLBCL, Diffuse large B cell lymphoma;

BL, Burkitt's lymphoma; FL, Follicular lymphoma; PTCL, Peripheral T-cell lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

Figure 2

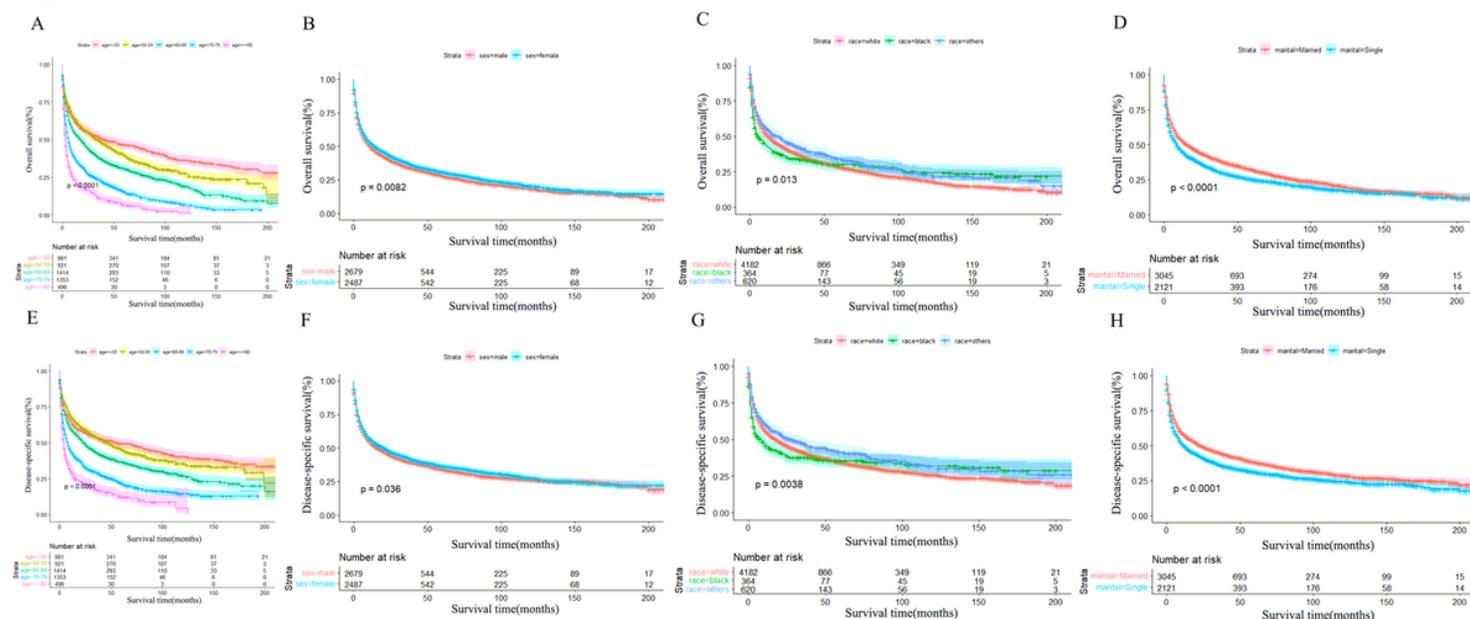


Figure 2

Survival analysis of primary central nervous system lymphoma stratified by age, sex, race, marital status. Significant statistical difference was found in OS with age (A), P<0.0001, sex (B), P=0.0082, race (C), P=0.0013, and marital status (D), P<0.0001. Significant statistical difference was found in DSS with age (E), P<0.0001, sex (F), P=0.036, race (G), P=0.0038, and marital status (H), P<0.0001. Inferior OS and DSS was significantly associated with elder age, male, black, and single.

Figure 3

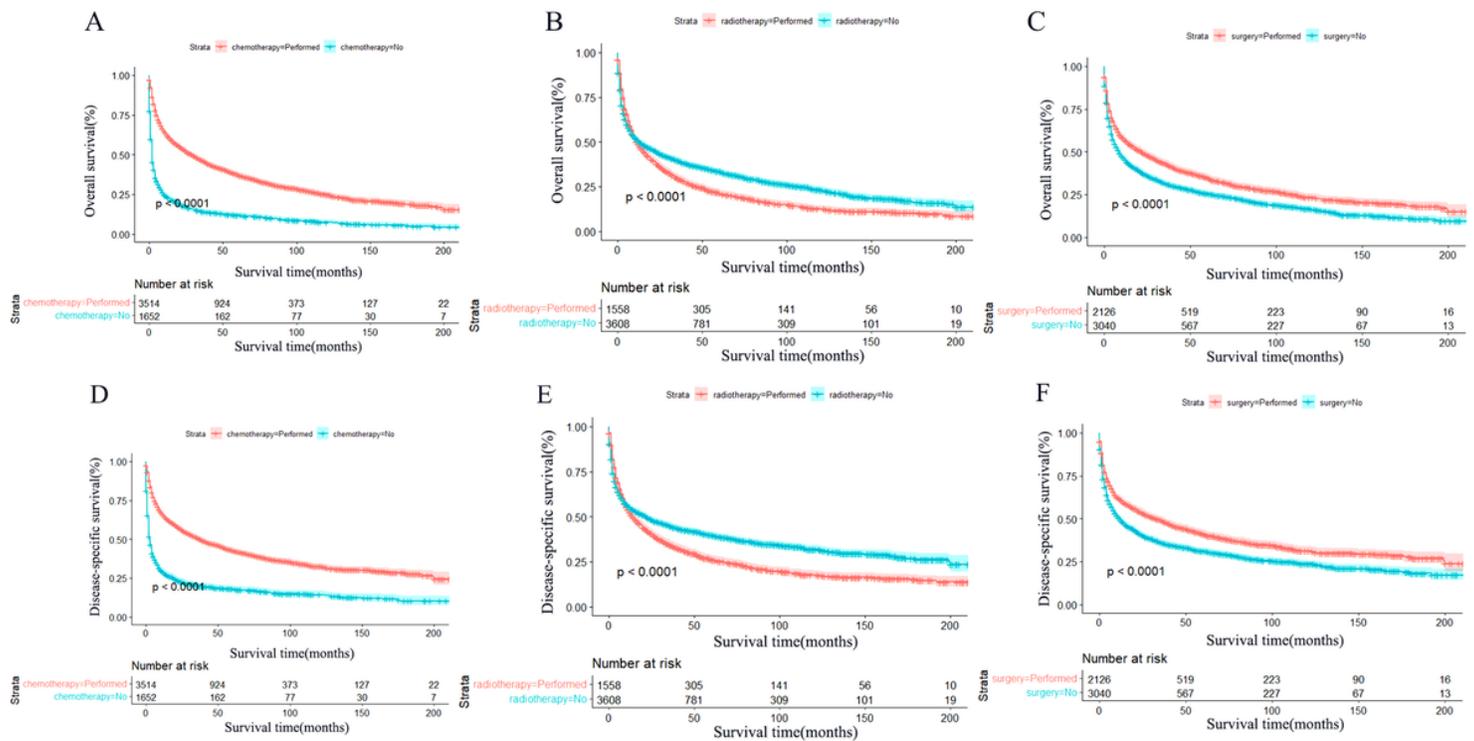


Figure 3

Survival analysis of primary central nervous system lymphoma stratified by treatment: chemotherapy, radiotherapy and surgery. Significant statistical difference was found in OS and DSS between patients with chemotherapy and no chemotherapy (A, D), radiotherapy and no radiotherapy (B, E), surgery and no surgery (C, F), $P < 0.0001$. Patients who underwent chemotherapy and surgery achieved significantly longer OS and DSS compared to who did not. However, radiotherapy led to worse OS and DSS in the long-term.

Figure 4

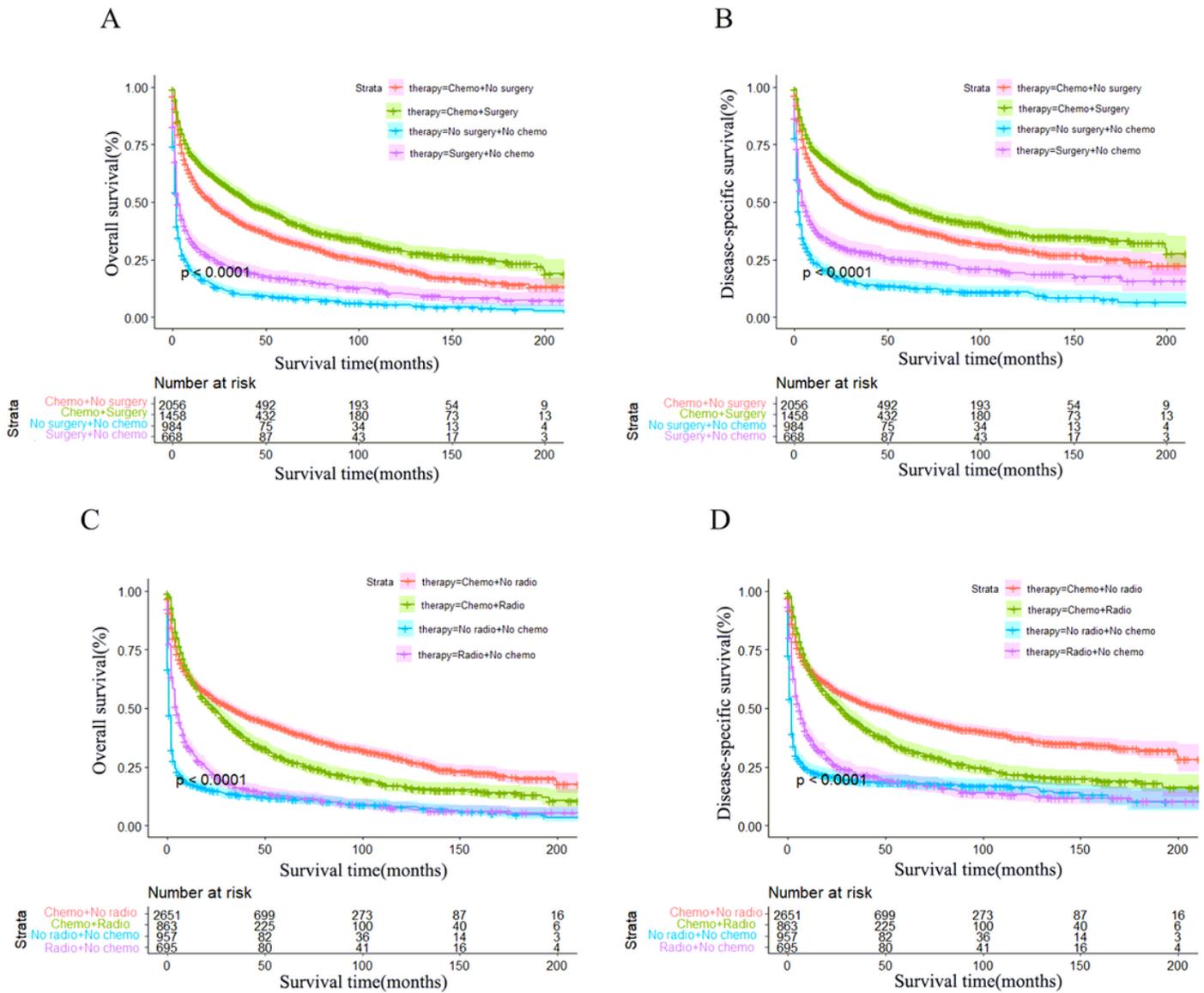


Figure 4

Effect of combination therapy on primary central nervous system lymphoma. Kaplan-Meier survival curves of combined effect of chemotherapy and surgery: OS (A) and DSS (B), chemotherapy and radiotherapy: OS (C) and DSS (D). The surgery combined with chemotherapy was significantly associated with better OS and DSS, $P < 0.0001$. Chemotherapy combined with radiotherapy was associated with better OS and DSS in the early stage of the treatment, however, the long-term OS and DSS were not superior to chemotherapy alone, $P < 0.0001$.

Figure 5

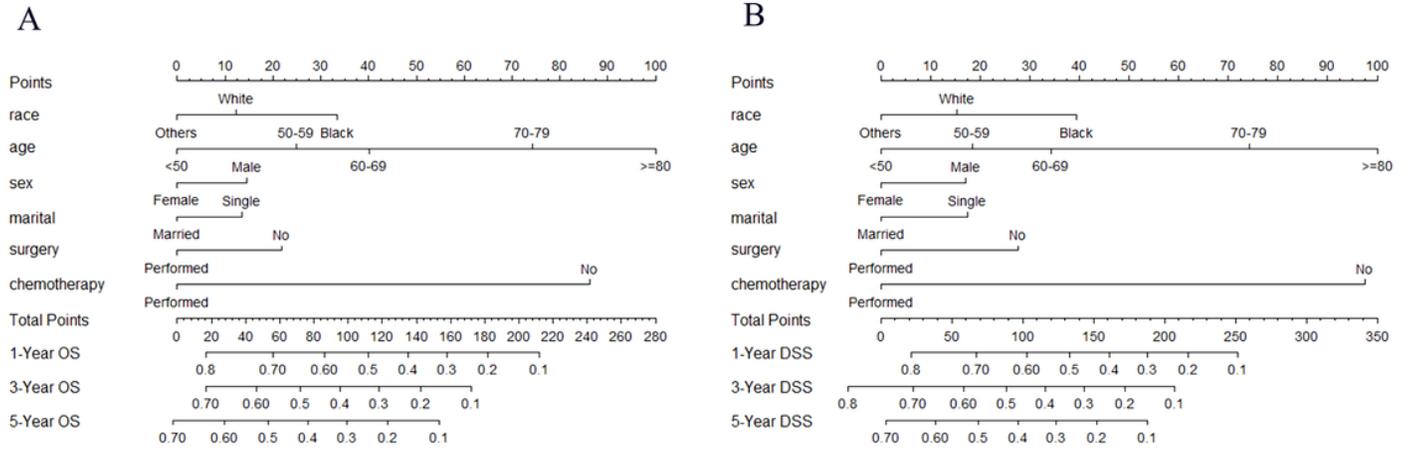


Figure 5

Nomogram to predict 1-, 3-, and 5-year OS (A) and DSS (B) probability in patients with primary central nervous system lymphoma. The OS and DSS rates at 1-, 3-, and 5- year can be predicted by integrating scores related to race, age, sex, marital, surgery, chemotherapy, and projecting the total points to the bottom scale.

Figure 6

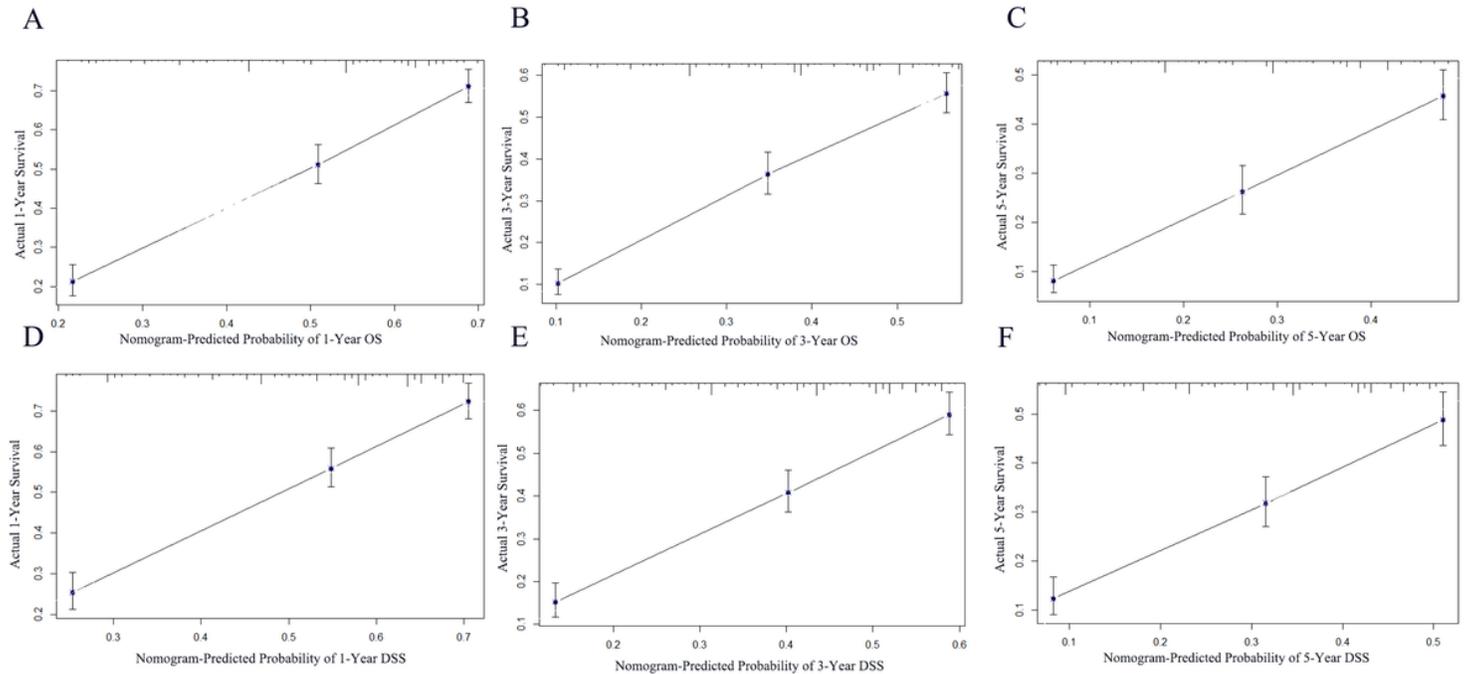


Figure 6

Calibration curve of the nomogram for the prediction of 1-, 3- and 5-year OS (A-C) and DSS (D-F). The abscissa represents nomogram-predicted survival rate, ordinate represents actual survival rate, and the calibration curves for 1-, 3-, and 5-year survival rate showed satisfactory agreements between the predicted and actual values.

Figure 7

A
Dynamic Nomogram

race
White

age
70-79

sex
Male

marital
Married

surgery
Performed

chemotherapy
Performed

Predicted Survival at this Follow Up:

time
0 36 225

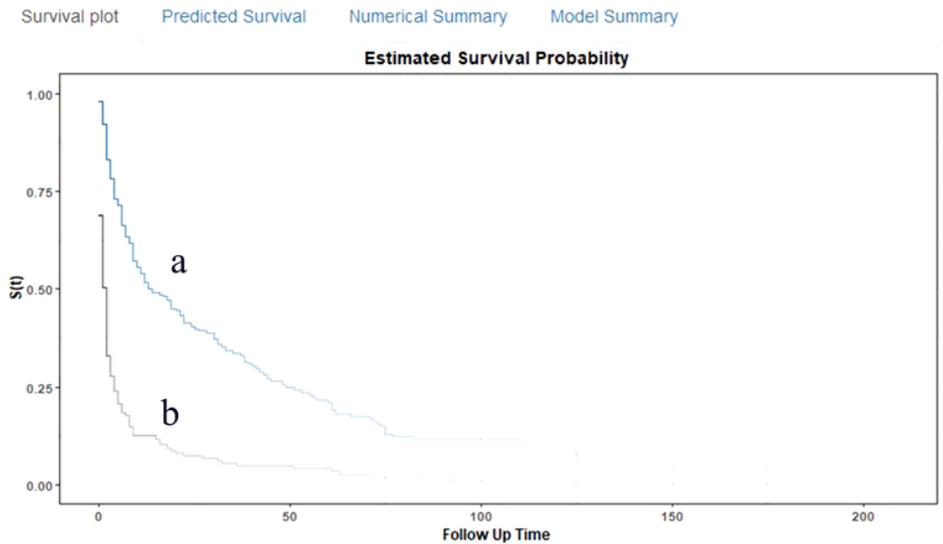
Alpha blending (transparency)

Predict

Press Quit to exit the application

Quit

B



C

time	race	age	sex	marital	surgery	chemotherapy	Prediction	Lower.bound	Upper.bound
1	36	White	70-79	Male	Married	No	No	0.047	0.022 0.101
2	36	White	70-79	Male	Married	Performed	Performed	0.340	0.272 0.420

Figure 7

An example to illustrate the use of the web-based survival rate calculator. (A) a 75-year-old married white man was diagnosed as PCNSL with DLBCL, if he refused chemotherapy and surgery, his 3-year OS rate is approximately only 4.7% (95% CI 0.022-0.101), if he was given chemotherapy and surgery, his 3-year OS rate is approximately 34.0% (95% CI 0.272-0.420). (B) His survival curve depending on whether he was treated or not: received treatment (a), refused treatment (b).