Original Article

Prognosis prediction model for a special entity of gastric cancer, linitis plastica

Xinhua Chen[1#], Yunfei Zhi[2#], Zhousheng Lin[2], Jinyuan Ma[3], Weiming Mou[2], Jiang Yu[1]

[1]Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]The First Clinical Medical School, Southern Medical University, Guangzhou, China; [3]The Second Clinical Medical School, Southern Medical University, Guangzhou, China

Contributions: (I) Conception and design: J Yu, X Chen, Y Zhi; (II) Administrative support: J Yu, X Chen; (III) Provision of study materials or patients: J Ma; (IV) Collection and assembly of data: Y Zhi, J Ma; (V) Data analysis and interpretation: X Chen, Y Zhi, W Mou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Jiang Yu, MD, PhD. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Email: balbc@163.com; balbcyujiang@163.com.

Background: Gastric linitis plastica (GLP) is characteristic by its poor prognosis and highly aggressive characteristics compared with other types of gastric cancer (GC). However, the guidelines have not yet been distinguished between GLP and non-GLP.

Methods: A total of 342 eligible patients with GLP identified in the Surveillance, Epidemiology, and End Results (SEER) dataset were randomly divided into training set (n=298) and validation set (n=153). A nomogram would be developed with the constructed predicting model based on the training cohort's data, and the validation cohort would be used to validate the model. Principal component analysis (PCA) was used to evaluate the differences between groups. Cox regression and LASSO (least absolute shrinkage and selection operator) were used to construct the models. Calibration curve, time-dependent receiver operating characteristic (ROC) curve, concordance index (C-index) and decision curve analysis (DCA) were used to evaluate the predicting performance. Restricted mean survival time (RMST) was used to analyze the curative effect of adjuvant therapy.

Results: For patients in training cohort, univariable and multivariable Cox analyses showed that age, examined lymph nodes (LN.E), positive lymph nodes (LN.P), lesion size, combined resection, and radiotherapy are independent prognostic factors for overall survival (OS), while chemotherapy can not meet the proportional hazards (PHs) assumption; age, race, lesion size, LN.E, LN.P, combined resection and marital status are independent prognostic factors for cancer-specific survival (CSS). The C-index of the nomogram was 0.678 [95% confidence interval (CI), 0.660–0.696] and 0.673 (95% CI, 0.630–0.716) in the training and validation cohort, respectively. Meanwhile, the C-index of the CSS nomogram was 0.671 (95% CI, 0.653–0.699) and 0.650 (95% CI, 0.601–0.691) in the training and validation cohort for CSS, respectively. Furthermore, the nomogram was well calibrated with satisfactory consistency. RMST analysis further determined that chemotherapy and radiotherapy might be beneficial for improving 1- and 3-year OS and CSS, but not the 5-year CSS.

Conclusions: We developed nomograms to help predict individualized prognosis for GLP patients. The new model might help guide treatment strategies for patients with GLP.

Keywords: Gastric cancer (GC); linitis plastica; adjuvant treatment; risk prediction

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Introduction

Although the morbidity and mortality of gastric cancer (GC) have been declined in decades, it remains the third leading cause of cancer-related death (1,2). With a long history, the gastric linitis plastica (GLP) is a unique entity of GC with the entity of cellular spread to the submucosal and muscular layers (3-5). In comparison with other types of GC, GLP has been commonly reported to have a poor prognosis with a median overall survival (OS) duration ranges from 6 to 14 months, indicating that GLP does have its special prognostic significance (6-13). Correspondingly, the biological behavior of GLP is revealed to have a propensity toward involvement of the entire stomach, invasion of the gastric serosa, peritoneal seeding, and massive lymph node metastases (4,5).

However, due to the indiscriminately use of terms such as signet ring cell carcinoma, Lauren diffuse adenocarcinoma, Borrmann type IV cancer, scirrhous cancers, the definition of GLP is still controversial (5). Furthermore, the reports addressing the treatment of the distinct type GC is quite limited. Currently, staging and treatment guidelines for gastric adenocarcinoma do not differentiate between GLP and non-GLP (14). Some clinical studies have demonstrated that surgical treatment has a handsome effect on improving the prognosis of GLP patients (6-9,11,13), which is consistent with the results of our previous research that showed gastrectomy was associated with an overwhelming survival advantage.

Considering the speciality of biologic behavior of GLP mentioned above, the GLP's response to adjuvant treatments may differ from non-GLP theoretically. However, the predictive model to assess the effect of treatment for GLP is still limited. Therefore, it's necessary to investigate the benefit of each treatment strategy and construct a model to predict the prognosis of GLP patients performed with gastrectomy exclusively, thus define the optimum therapeutic tactic for them. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-264).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No formal approval is required as data were collected from a source that was publicly available and did not contain unique patient identifiers. We obtained permission to access research data files of Surveillance, Epidemiology, and End Results (SEER) database. Given that these data are de-identified and ethics approval is waived, the study did not require informed consent.

Data source and selection criteria

Patient data of GC, including the GLP, were retrieved from the National Cancer Institute's SEER population-based data registry.

Data of the patients with GLP from 1988 to 2016 were obtained from the SEER database following the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) where GLP was coded as 8142/3, 12/31/2016 was the cut-off date in this study.

The patient selection standard consistent with the criteria of the SEER database contains:

(I) confirmed by pathological examination with active follow-up;
(II) confirmed to have undergone gastrectomy;
(III) exclusion of patients <18 years old;
(IV) exclusion of patients with unknown survival months or indefinite endpoint;
(V) exclusion of patients with unclear TNM stage or tumor size.

Following these criteria, 124,775 GC patients were identified from the database, and eventually leaving 342 GLP patients in the final cohort for analysis (*Figure 1*).

The demographics data were defined by the county attributes from the US Census 2010–2016 American Community Survey 5-year data files, which we could get from the SEER. Stat software.

Study variables

The following patients' information was used in our study: Baseline demographics including gender, age, race, origin code, marital status, residence type, insurance situation, bachelor education, median household income and survival months; Tumor features including tumor size, pathology grade, primary tumor invasion, node status, examined lymph nodes (LN.E), positive lymph nodes (LN.P) and tumor location; Treatment information including gastrectomy, and additional therapy (chemotherapy, radiotherapy). The X-tile program (Yale University School of Medicine, New Haven, CT, USA) was used to find the best cut-off point for the continuous variables, including Age, LN.E, and LN.P. All TNM classifications were restaged according to the criteria described in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition, 2017.

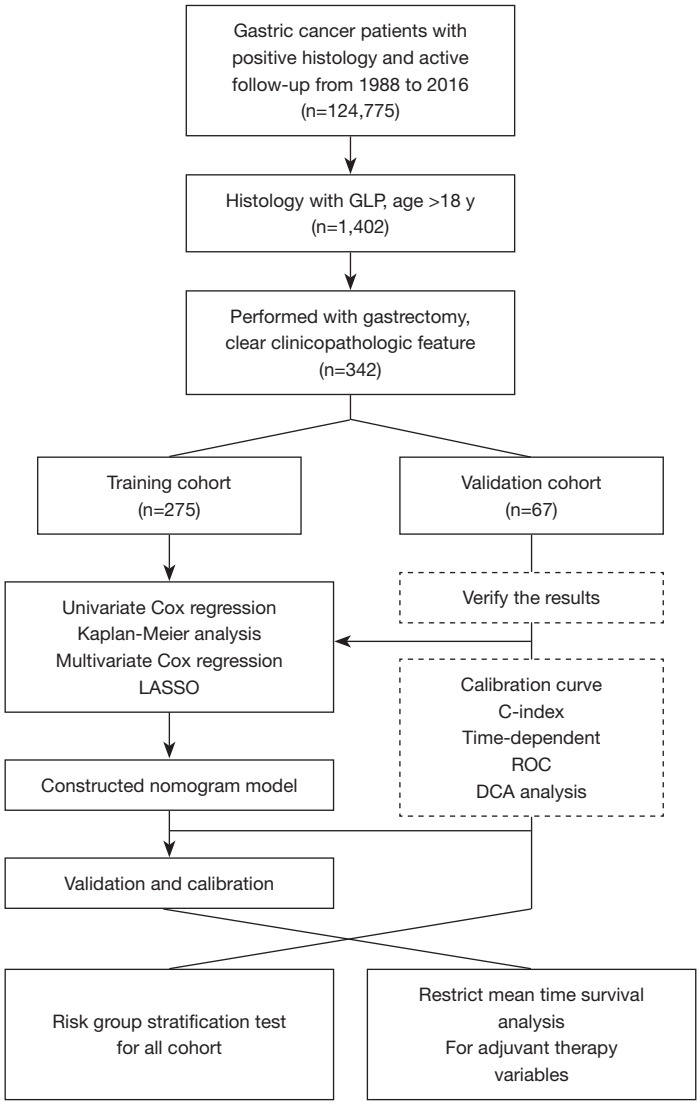

Figure 1 Study diagram flow of our research. GLP, gastric linitis plastica; LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic; DCA, decision curve analysis.

The main study endpoints include the OS and cancer-specific survival (CSS). The CSS defined as the time from the diagnosis to death attributed to GC as censoring was used as the main evaluation index of survival efficacy and OS, which is defined as from the date of operation to the date of death or the latest follow-up is used to analyze as well.

Statistical analysis and nomogram construction

The data of patients who underwent gastrectomy (n=342) were used to construct and validate the GLP predicting model. To make better use of our data, a higher ratio of training cohort has been made, and a considerable number of patients have been kept for validation. After all, the enrolled eligible patients were randomly assigned to the training cohort and validation cohort by simple random sampling with caret package. Principal component analysis (PCA) is used to evaluate the consistency between the training cohort and validation cohort.

Descriptive statistics were used to calculate the absolute number and frequency among patients with GLP at the time of cancer diagnosis. The χ^2, t, or Fisher exact test is used for interclass comparison when appropriate.

For survival analysis, the OS and CSS were estimated

by the Kaplan-Meier (K-M) method and tested by log-rank test. Univariate Cox proportional hazards (PHs) regression was performed to identify potential prognostic factors. Meanwhile, LASSO (least absolute shrinkage and selection operator), a machine learning method that can perform variable selection and regularization while fitting a multivariate Cox proportional regression model, would be used to simultaneously locate the valuable potential prognostic factors and avoid collinearity further (15). After synthesizing the results of univariate Cox regression and LASSO, the selected independent risk factors would be used to construct the GLP predicting model via multivariate Cox PHs regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk factors were also calculated.

Nomogram is an excellent tool widely used for the visualization of tumor prognosis prediction models. A nomogram would be developed with the constructed GLP predicting model based on the training cohort's data, and the data of the validation cohort would be used to validate the model in concern of model overfitting or underfitting. Hmisc, survival and rms packages were used in our research. Based on the predictive models with the selected identified prognostic factors, nomograms were constructed for predicting 1-, 3- and 5-year OS and CSS. The calibration curve, time-dependent receiver operating characteristic (ROC) curve, concordance index (C-index), and decision curve analysis (DCA) were used to evaluate the performance of the models. Calibration curves were constructed to avoid overfitting by comparing the mean of predicted and observed survival with the K-M method. A time-dependent ROC curve was drawn to evaluate the accuracy of the nomogram (16), Harrell's C-index was used to evaluate the discrimination (17). Decision Curve Analysis was used to evaluate the actual clinical value of our model, meanwhile, a simple model based on TNM stage was established for comparison as well (18). To further illustrate the discrimination ability of the models, we classified the population into low-, medium- and high-risk subgroups according to the total risk scores calculated via nomogram. Meanwhile, respective K-M survival curves in each stage were depicted. To evaluate the performance of adjuvant therapy better, restricted mean survival time (RMST) was used to analyze the actual curative effect of chemotherapy & radiotherapy (19). One-, 3-, and 5-year were selected to be the cut-off timepoint of RMST analysis. Data analyses and model construction were performed using R 3.6.1 (R foundation, Vienna, Austria). The results were considered statistically significant when P<0.05 on both sides.

Results

Patient characteristics

For 342 GLP patients who underwent gastrectomy, the average follow-up time of all patients is 78.3 months. All patients were randomly divided into a training set, including 275 patients (80%) and a validating set containing 67 patients (20%) for model construction and validation. The oncological and clinical characteristics of these two sets were shown in *Table 1*. The result of PCA and K-M analyses indicates that there's no apparent overall difference between the groups (shown in Figure S1).

Independent prognostic factors for OS and CSS

For patients in training cohort, univariate Cox analyses were used to identify the potential prognostic factors associated with OS and CSS. Age (P<0.05),lesion size (P<0.001), primary tumor invasion (P=0.002), LN.E (P=0.006), LN.P (P<0.001), combined resection (P=0.010), chemotherapy (P<0.05), radiotherapy (P<0.001) and martial status (P<0.05) are potential prognostic factors for OS; age (P<0.001), race (P<0.05), lesion size (P<0.001), primary tumor invasion (P<0.01), node status (P<0.001), LN.E (P<0.015), LN.P (P<0.001), combined resection (P<0.05), and radiotherapy (P<0.05) are potential prognostic factors for CSS. Meanwhile, LASSO was used to reselect and penalize variables to avoid under-fitting or over-fitting data by 10-fold cross-validation (Figure S2), results were summarized in *Tables 2,3*.

Finally, after synthesizing the results of univariate Cox regression and Lasso, all independent risk factors that met the PH assumption test were entered into multivariate Cox regression analysis further. The results revealed that age, lesion size, LN.E, LN.P, combined resection, and radiotherapy should be included in the OS model, while age, race, lesion size, LN.E, LN.P, combined resection, and marital status were chosen to build the CSS model. K-M method was used to draw the survival curves of selected prognostic factors (Figures S3,S4). The data of our analysis were summarized in *Tables 2,3*, respectively.

Prognostic nomogram construction, calibration, validation, and simplified evaluation

Based on the results of multivariate Cox regressions, nomograms were constructed to facilitate the assessment of the prognosis of patients performed with gastrectomy (*Figure 2*). Compared with other clinicopathologic features,

Table 1 Patients characteristics

Variables	All cohort	Training cohort		Validation cohort	
		No.	%	No.	%
Number of cases	342	275	80	67	20
Year at diagnosis					
1998–2007	356	202	73	54	80
2008–2016	86	73	27	13	20
Sex					
Male	169	134	49	35	52
Female	173	141	51	32	48
Age, y					
<45	42	31	11	11	16
≥45, ≤81	268	216	79	52	78
>81	32	28	10	4	6
Race					
White	231	183	67	48	72
Black	41	34	12	7	10
Others	72	58	21	14	21
Origin recode NHIA					
Non-Spanish-Hispanic-Latino	254	210	76	44	66
Spanish-Hispanic-Latino	88	65	24	23	34
Tumor location					
Upper stomach	31	24	9	7	10
Middle stomach	26	19	7	7	10
Lower stomach	76	61	22	15	22
Lesser curvature	24	18	7	6	9
Greater curvature	11	10	4	1	1
Overlapping lesion	89	77	28	12	18
Stomach, NOS	85	66	24	19	28
Lesion size					
<5 cm	37	32	12	5	7
≥5 cm	305	243	88	62	93
Grade					
G1–2	6	5	2	1	1
G3–4	307	246	89	61	91
Unknown	29	24	9	5	7
Primary tumor invasion					

Table 1 (*comtimued*)

Table 1 (*comtimued*)

Variables	All cohort	Training cohort		Validation cohort	
		No.	%	No.	%
T1–3	37	32	12	5	7
T4	305	243	88	62	93
Node status					
N0	65	54	20	11	16
N+	277	221	80	56	84
Examined lymph nodes (LN.E)					
No	21	13	5	8	12
Yes	321	262	95	59	88
Positive lymph nodes (LN.P)					
0	83	66	24	17	25
≤15	210	165	60	45	67
>15	49	44	16	5	7
Gastrectomy					
Total gastrectomy	167	136	49	31	46
Partial gastrectomy	64	54	20	10	15
Gastrectomy, NOS	111	85	31	26	39
Combined resection					
Yes	85	72	26	13	19
No	257	203	74	54	81
Chemotherapy					
No	158	130	47	28	42
Yes	184	145	53	39	58
Radiotherapy					
No	225	182	66	43	64
Yes	117	93	34	24	36
Marital status					
Non-married	120	95	35	25	37
Married	209	168	61	41	61
Unknown	13	12	4	1	1
Insurance					
Insured	87	78	28	9	13
Uninsured	2	2	1	0	0
Any medical	17	12	4	5	7
Unknown	236	183	67	53	79

Table 1 (*comtimued*)

Table 1 (*comtimued*)

Variables	All cohort	Training cohort		Validation cohort	
		No.	%	No.	%
Bachelor education					
<30%	111	93	34	18	27
≥30	231	182	66	49	73
Median house incomes (per $40,000 incomes)					
0–40,000	9	6	2	3	4
40,000–80,000	237	194	71	43	64
60,000–120,000	96	75	27	21	31

Table 2 Univariate Cox regression analyses, LASSO coefficient score, and multivariate Cox regression analyses of risk factors for OS

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
Year at diagnosis				0.284						
1998–2007										
2008–2016	0.851	0.633	1.143							
Sex										
Male										
Female	1.180	0.919	1.515	0.194						
Age, y				<0.001	0.317				<0.001	
<45										0
≥45, ≤81	1.625	1.053	2.507	0.028		1.463	0.939	2.278	0.0.09	2.76
>81	3.089	1.753	5.444	<0.001		3.9608	2.20	7.14	<0.001	10
Race										
White										
Black	0.816	0.546	1.220	0.321						
Others	1.252	0.920	1.704	0.152						
Origin										
Non-Spanish-Hispanic-Latino										
Spanish-Hispanic-Latino	0.921	0.686	1.236	0.584						
Lesion size				0.001	0.362				0.006	
<5 cm										0
≥5 cm	2,288	1.457	3.593	<0.001		1.933	1.212	3.084	0.006	4.87
Grade				0.438						

Table 2 (*comtimued*)

Table 2 (*comtimued*)

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
G1–2										
G3–4	0.804	0.331	1.955	0.631						
Unknown	0.603	0.224	1.627	0.318						
Primary tumor invasion				0.002	0.080				0.262	
T1–3										0
T4	1.596	1.192	2.137			1.190	0.878	1.613	0.262	1.27
Node status				<0.001	0.125				0.669	
N0										0
N+	2.154	1.511	3.071			0.826	0.344	1.983	0.669	1.42
Retrieved nodes				0.006	–0.094					
No										6.39
Yes	0.454	0.259	0.796			0.415	0.203	0.848	0.016	0
Positive nodes				<0.001	0.242				0.016	
0										0
≤15	1.739	1.251	2.419	0.001		2.293	1.013	5.192	0.046	6.15
>15	2.837	1.864	4.316	<0.001		3.208	1.360	7.566	0.007	8.69
Gastrectomy				0.189						
Total										
Non-total	0.729	0.520	1.023	0.068						
Unknown	0.921	0.690	1.228	0.574						
Combined resection				0.010	0.096				0.012	
No										0
Yes	1.443	1.090	1.911			1.463	1.086	1.983	0.012	2.79
Chemotherapy				0.019	–0.050					
No										
Yes	0.741	0.577	0.952							
Radiotherapy				0.001	–0.161				0.008	
No										2.74
Yes	0.641	0.491	0.836			0.692	0.527	0.910		0
Marital status				0.027						
Unmarried										
Married	0.701	0.538	0.912	0.008						

Table 2 (*comtimued*)

Table 2 (*comtimued*)

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
Unknown	0.932	0.498	1.744	0.825						
Insurance situation				0.492						
Insured										
Uninsured	0.784	0.192	3.205	0.734						
Any medical	0.789	0.392	1.585	0.505						
Unknown	1.168	0.876	1.557	0.291						
Bachelor education				0.732						
<30%										
≥30	0.853	0.732	1.240							
Median house incomes (per $40,000 incomes)				0.632						
0–40,000										
40,000–80,000	0.684	0.281	1.670	0.405						
80,000–120,000	0.740	0.298	1.841	0.517						

LASSO, least absolute shrinkage and selection operator; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 3 Univariate Cox regression analyses, LASSO coefficient score, and multivariate Cox regression analyses of risk factors for CSS

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
Year at diagnosis				0.090						
1998–2007										
2008–2016	0.741	0.525	1.048							
Sex				0.270						
Male										
Female	1.173	0.884	1.556							
Age, y				0.001	0.276				<0.001	
>81	1.309	1.493	4.916	0.001		3.061	1.893	4.950	<0.001	8.43
Race				0.036	0.008				0.046	
White										
Black	0.776	0.483	1.246	0.293		0.727	0.434	1.218	0.226	2.53
Others	1.396	1.027	2.009	0.035		1.380	0.980	1.961	0.065	0
Origin				0.669						4.92

Table 3 (*comtimued*)

Table 3 (*comtimued*)

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
Non-Spanish-Hispanic-Latino										
Spanish-Hispanic-Latino	1.072	0.778	1.447							
Lesion size				<0.001	0.470				0.003	
<5 cm										0
≥5 cm	2.692	1.557	4.656	<0.001		2.315	1.321	4.058	0.003	6.18
Grade				0.420						
G1–2										
G3–4	0.804	0.298	2.173	0.668						
Unknown	0.565	0.184	1.735	0.319						
Primary tumor invasion				0.007	0.042				0.663	
T1–3										0
T4	1.567	1.128	2.177	0.007		1.079	0.768	1.516	0.663	0.53
Node status				<0.001	0.191				0.754	
N0										2.11
N+	2.309	1.534	3.477	<0.001		0.754	0.254	2.240	0.611	0
Retrieved nodes				0.015	–0.123				0.010	
No										9.13
Yes	0.451	0.238	0.856	0.015		0.291	0.114	0.743	0.010	0
Positive nodes				<0.001	0.220				0.030	
0										0
≤15	1.836	1.259	2.678	0.002		2.772	0.982	7.828	0.054	7.56
>15	2.944	1.823	4.755	<0.001		3.841	1.316	11.213	0.010	10
Combined resection				0.013	0.129				0.012	
No										3.27
Yes	1.494	1.089	2.050	0.013		1.552	1.100	2.189	0.012	0
Gastrectomy				0.247						
Non-total	0.727	0.494	1.071	0.107						
Nos	0.982	0.710	1.357	0.911						
Chemotherapy				0.215						
No										
Yes	0.836	0.629	1.110							
Radiotherapy				0.035	–0.06					

Table 3 (*comtimued*)

Table 3 (*comtimued*)

Variables	Univariate				LASSO	Multivariate				
	HR	95% CI		P	Score	HR	95% CI		P	Score
		Lower	Upper				Lower	Upper		
No										
Yes	0.728	0.542	0.978							
Marital status				0.057	–0.012				0.102	
Unmarried										2.478
Married	0.697	0.518	0.938	0.017		0.717	0.529	0.973	0.033	0
Unknown	0.745	0.343	1.621	0.458		0.785	0.357	1.726	0.547	0.645
Insurance situation				0.462						
Insured										
Uninsured	1.014	0.246	4.177	0.985						
Any medical	0.810	0.366	1.791	0.602						
Unknown	1.239	0.891	1.723	0.203						
Bachelor education				0.821						
<30%										
≥30%	0.966	0.716	1.304							
Median house incomes (per $40,000 incomes)				0.349						
0–40,000										
40,000–80,000	0.524	0.214	1.283	0.157						
80,000–120,000	0.565	0.225	1.418	0.224						

LASSO, least absolute shrinkage and selection operator; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

LN.E, LN.P, and lesion size conferred better impacts on OS and CSS for GLP patients performed with gastrectomy.

In training cohort, C-indexes were 0.678 (95% CI, 0.660–0.696) for OS and 0.671 (95% CI, 0.653–0.699) for CSS, which were superior to the seventh edition of TNM staging (OS: 0.561, 95% CI, 0.54–0.58, P<0.001; CSS: 0.61, 95% CI, 0.58–0.64, P<0.001). Meanwhile, in validation cohort, C-indexes were 0.673 (95% CI, 0.63–0.716) for OS and 0.650 (95% CI, 0.601–0.691) for CSS, also better than the seventh edition of TNM staging (OS: 0.56, 95% CI, 0.52–0.60, P<0.001; CSS: 0.57, 95% CI, 0.53–0.61, P<0.001).

The nomograms were both tested by 600 bootstraps resample for the internal validation, and 400 bootstraps resample for the external validation with the training cohort and validation cohort, respectively. The survival area under the curve (AUC) values of the ROC predicted the 1-, 3-, and 5-year OS of the nomogram to be 0.741, 0.773, and 0.839 in the training cohort. Meanwhile, the AUC values of 1-, 3-, and 5-year CSS of the nomogram are to be 0.703, 0.751, and 0.822, respectively, indicating good agreements between prediction and practical observation; besides, the result of the validation set is also shown. DCA was performed to evaluate the predicting probability of our models. In comparison with the simple model based on the TNM stage, our model performed much better in practice. Calibration curves, time-dependent ROC curves, and DCA curves of the training cohort and the validation cohort are presented in *Figures 3*,*4*.

The nomogram scores of every including variable were listed in *Table 4*. Meanwhile, to evaluate the actual discrimination ability of our model further, the nomogram scores were calculated for all patients. Then, patients were

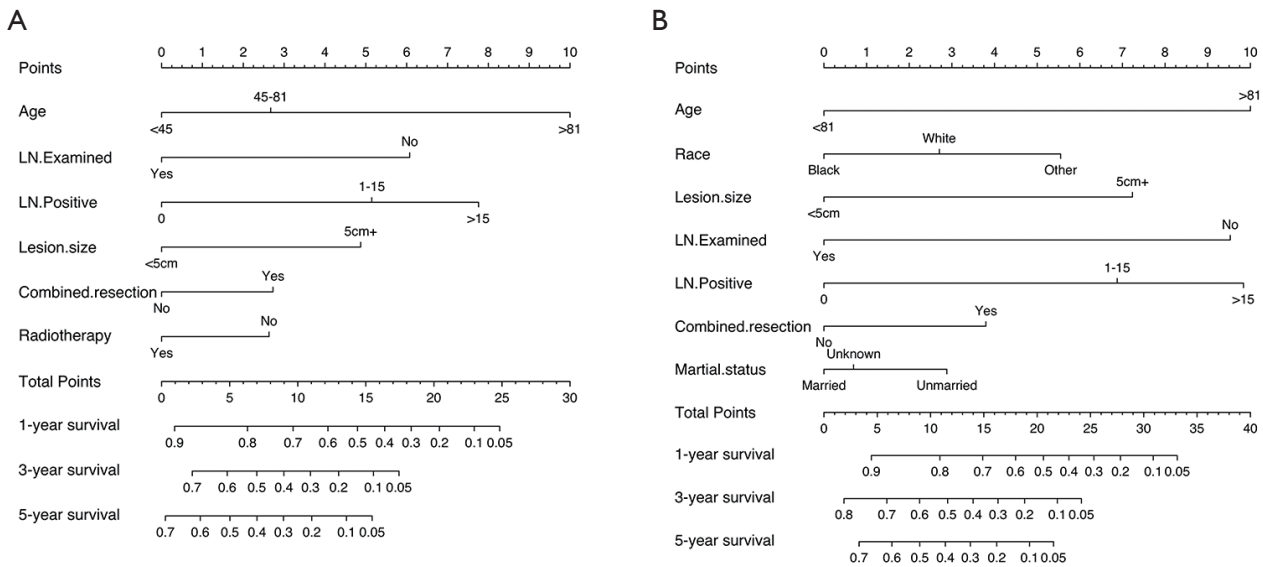

Figure 2 Prognostic nomogram predicting the probability of 1-, 3-, and 5-year OS rate (A) and CSS (B) in patients with surgical resected GLP. GLP, gastric linitis plastica; OS, overall survival; CSS, cancer-specific survival; LN, lymph node.

stratified into the low-risk group (OS: 110/342, 31%, score: 0–11; CSS: 108/342, 31%, score: 0–17), medium-risk group (OS: 135/342, 39%, score: 11–15; CSS: 139/342, 39%, score: 17–23), and high-risk group (OS: 101/342, 30%, score: >15; CSS: 101/342, 30%, score: >23). The stratification strategy was summarized in *Table 4*. The K-M curves showed that OS & CSS in the different groups was accurately differentiated by the risk stratification strategy (shown in *Figure 5*), indicating the nomogram's outstanding discrimination ability for GLP.

Survival analysis based on RMST

Although the Cox analyses have shown that chemotherapy (P<0.05), radiotherapy (P<0.001) was associated with superior prognosis, the K-M curves, log-rank test and PHs assumption test showed that chemotherapy and radiotherapy cannot meet the PH assumption (*Figure 6*). Therefore, it is unstable to evaluate these variables with traditional method (*Figure 6*). To evaluate the actual therapeutic effect of adjuvant therapy, RMST within the truncation time of 1-, 3-, and 5-year were calculated to compare further survival in the patients received adjuvant therapy or not. The results were summarized in *Tables 5*,*6*, Figures S5,S6. For CSS (*Table 5* & Figure S5), within the 3 years, on average, patients received chemotherapy would survive 3.2 months longer than the patients not received chemotherapy (19.6 *vs.* 16.4 months, P=0.028); consistently, patients received radiotherapy would survive 4.3 months longer than the patients not received chemotherapy (21.0 *vs.* 16.6 months, P<0.001). However, within 5 years, on average, patients received chemotherapy would not significantly gain superior survival (23.7 *vs.* 20.9 months, P=0.237); similarly, patients received radiotherapy also would not significantly gain superior survival (25.1 *vs.* 21.1 months, P=0.100). While for OS (*Table 6* & Figure S6), either the patients received chemotherapy or radiotherapy gain a better prognosis within the truncation time of 1-, 3-, and 5-year.

Discussion

GLP made features of poor prognosis and highly aggressive characteristics compared with other types of GC. Our validations focused on GLP patients performed with gastrectomy exclusively and revealed the passable performance of our nomogram in prognosis prediction. And this is the first prognosis predictive model designed for GLP patients. To better detect prognosis prediction model for GLP, time-dependent ROC curve and DCA curve are also used to analyze the actual distinguishing ability of the model. Encouragingly, the ROC is higher than 0.75 and the DCA curve indicated that this model has better prediction ability in practice. In other words, it was well calibrated

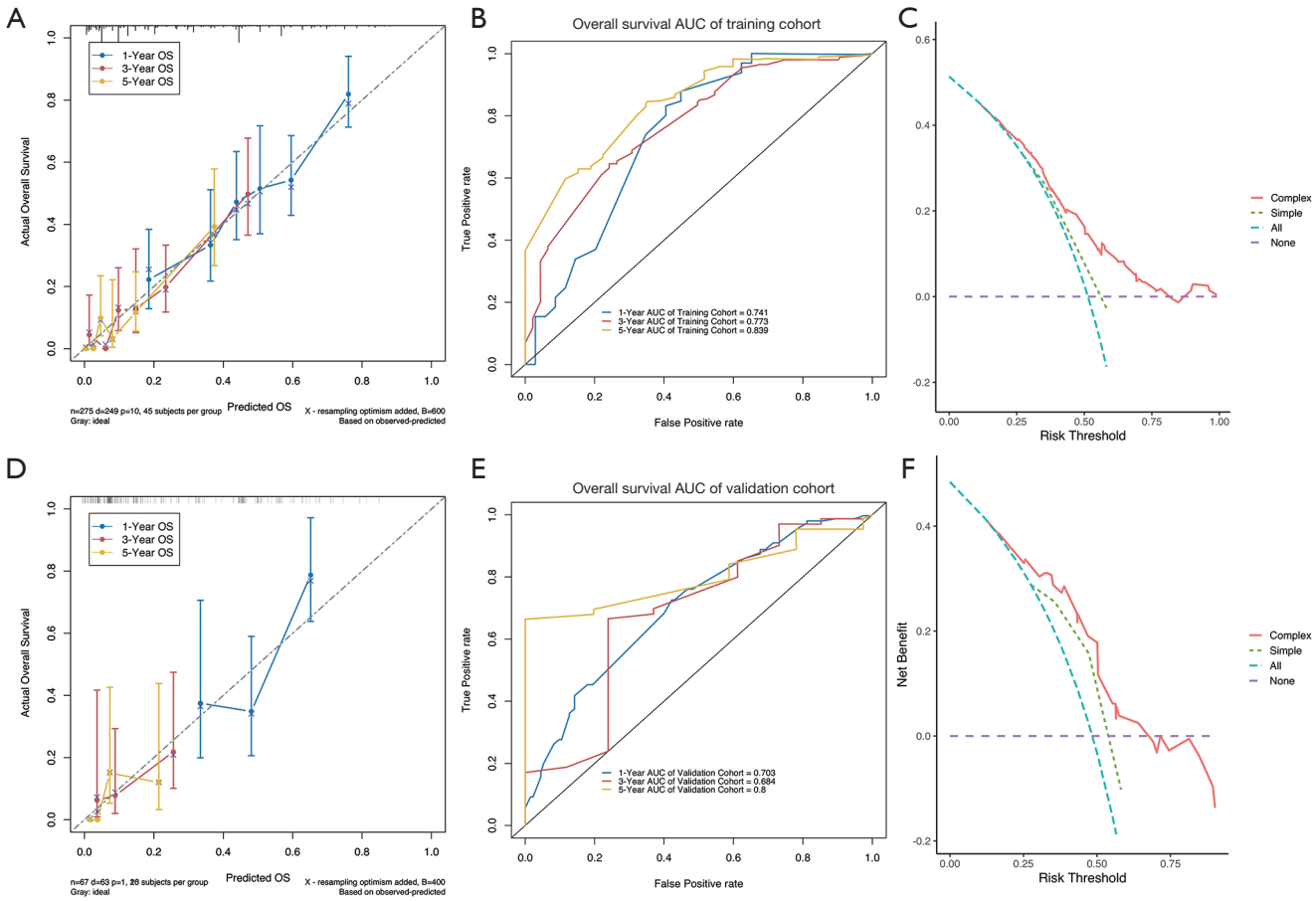

Figure 3 Multidimensional evaluation of our OS nomogram model. (A) Calibration curves of OS nomogram using training cohort; (B) time-dependent ROC curves of OS nomogram using training cohort; (C) DCA curves of OS nomogram using training cohort; (D) calibration curves of OS nomogram using validation cohort; (E) time-dependent ROC curves of OS nomogram using validation cohort; (F) DCA curves of OS nomogram using validation cohort. For calibration curves and time-dependent ROC curves, blue, red and yellow curves represent 1-, 3-, and 5-year analysis, prospectively. DCA curves were drawn to evaluate the practical performance of our model. The simple model was built based on TNM stage, while the complex model represents our nomogram model. OS, overall survival; ROC, receiver operating characteristic; DCA, decision curve analysis; AUC, area under the curve.

with satisfactory consistency. And in the GLP model, the characteristics of prognostic factors was consistent with non-GLP models. LN.E, LN.P, lesion size, combined resection, age, race and marital status have also been demonstrated to be independent prognostic factors in non-GLP cohort (20-23).

Further, since the guidelines have not yet been distinguished between GLP and non-GLP, we then focused on determining whether the respond of GLP to chemotherapy and radiotherapy is different form non-GLP or not.

Although the Cox analyses showed that chemotherapy ($P<0.05$), radiotherapy ($P<0.001$) was associated with superior prognosis, the PH assumption test presented that chemotherapy and radiotherapy were not in line with the PH hypothesis. Thus, we introduced a new method of RMST, which does not need to consider the PH assumption, to specifically explore the actual effects of radiotherapy and chemotherapy. Notably, the deeper analysis suggested that both chemotherapy and radiotherapy may play important roles in improving outcomes for GLP within the truncation time of 1- and 3-year, but the advantages of CSS lost for the truncation time of 5-year both in chemotherapy and radiotherapy, which gives additional new knowledge to the

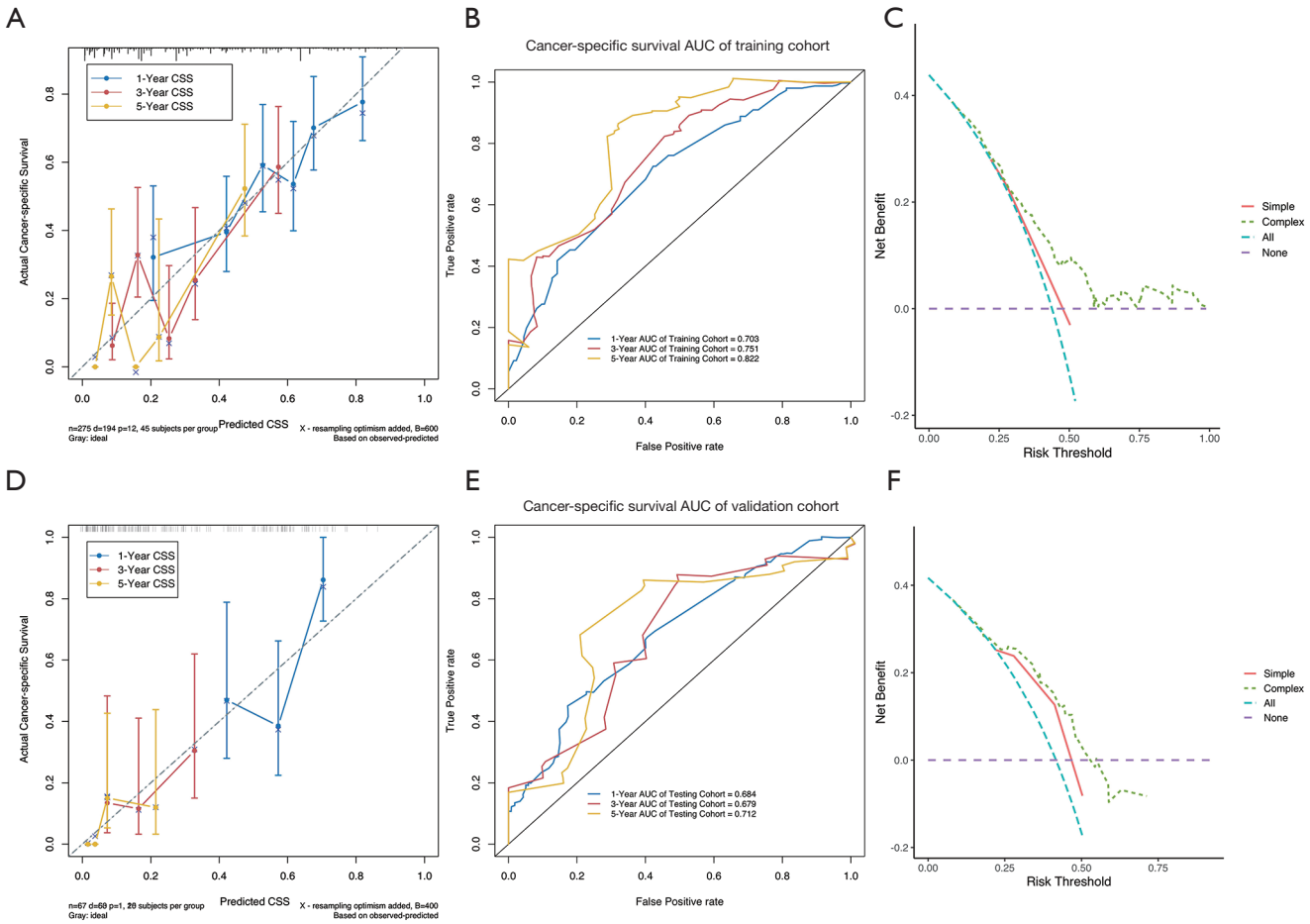

Figure 4 Multidimensional evaluation of our CSS nomogram model. (A) Calibration curves of CSS nomogram using training cohort; (B) time-dependent ROC curves of CSS nomogram using training cohort; (C) DCA curves of CSS nomogram using training cohort; (D) calibration curves of CSS nomogram using validation cohort; (E) time-dependent ROC curves of CSS nomogram using validation cohort; (F) DCA curves of CSS nomogram using validation cohort. For calibration curves and time-dependent ROC curves, blue, red and yellow curves represent 1-, 3-, and 5-year analysis, prospectively. DCA curves were drawn to evaluate the practical performance of our model. The simple model was built based on TNM stage, while the complex model represents our nomogram model. CSS, cancer-specific survival; ROC, receiver operating characteristic; DCA, decision curve analysis; AUC, area under the curve.

existing literature. Since CSS is a more specific indicator than OS to evaluate the oncological effect of chemotherapy and radiotherapy for GLP, the inconsistency between 1- and 3-year CSS and 5-year CSS potentially indicated that chemotherapy and radiotherapy were effective in the short run but developed resistance as the disease progress.

Many previous studies have demonstrated that chemotherapy conferred superior prognosis for GC (24-26). However, a previous study showed that GLP patients experienced poor responses to systemic therapy (27), likely because of the disease's scirrhous stromal component (5) which may protect cancer cells from the host's immune response and conventional chemotherapeutic agents (28-30). Besides, some fundamental researches have found angiogenesis, TGF-beta secretion and cell adhesion molecules might relate to the development of GLP disease and their poor prognosis (31-35). And these biological characteristics also could confer resistance to chemotherapy (36,37). Also, some studies have revealed that even microRNA might also work in modulating the sensitive to chemotherapy (38,39). There are also researches showing peripheral venous blood platelet-to-lymphocyte ratio

Table 4 Nomogram scores of OS nomogram model and CSS nomogram model

Prognostic factors and total scores	Score (OS)	Predicted 1-year OS	Score (CSS)	Predicted 1-year CSS
Age				
<45	0		0	
≥45, ≤81	2.7		0	
>81	10		8	
Race				
White			3	
Black			0	
Others			6	
Lesion size				
<5 cm	0		0	
≥5 cm	5		7	
Examined nodes				
No	6		10	
Yes	0		0	
Positive nodes				
0	0		0	
≤15	5.2		7	
>15	7.8		10	
Combined resection				
No	0		0	
Yes	2.7		4	
Radiotherapy				
No	2.6			
Yes	0			
Marital status				
Unmarried			3	
Married			0	
Unknown			1	
Total scores (OS)				
High risk (25%) >15		<45%		
Medium risk (50%) 11–15		45–65%		
Low risk (25%) 0–11		>65%		

Table 4 (*comtimued*)

Table 4 (*comtimued*)

Prognostic factors and total scores	Score (OS)	Predicted 1-year OS	Score (CSS)	Predicted 1-year CSS
Total scores (CSS)				
High risk (25%) >23				<40%
Medium risk (50%) 17–23				40–65%
Low risk (25%) <17				>65%

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

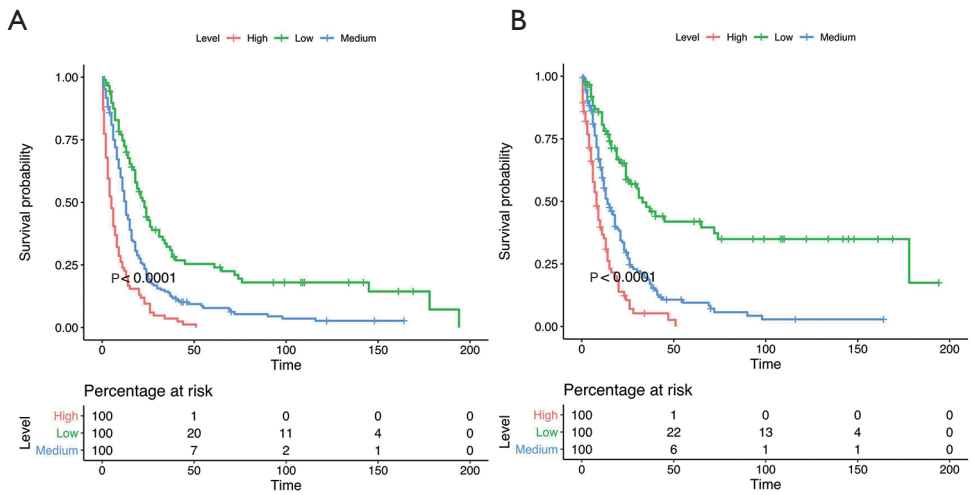

Figure 5 Risk group stratification of OS and CSS according to the nomogram model built with data of training cohort for all cohort. OS, overall survival; CSS, cancer-specific survival.

could predict the chemotherapy-sensitive (40). These studies implied that the response to chemotherapy is very complicated and may develop resistance as the disease progress. Thus, the respond of GLP to chemotherapy changed may be attributed to the tumor microenvironment developing. Addition, in the perspective of the clinic, the tumor cells of GLP are more prone to spread via lymphatic dissemination and by local extension into neighboring organs or as peritoneal carcinomatosis (8-11,14,41,42). The invasiveness of biological behavior and extensive tumor burden also make adjuvant chemotherapy work difficultly.

Like the effect of chemotherapy in our study, the radiotherapy also conferred a favored prognosis in the short run but developed resistance as the disease progress. While the Intergroup 0116 trial (43) has demonstrated that GC could get strong, persistent benefit from adjuvant radiochemotherapy, but the similar studies in GLP exclusively has not yet been reported. The difference between the results of GLP in our research and the results of GC in Intergroup 0116 trial may also be attributed to the special invasiveness of biological behavior of GLP. From the basis of molecular biology, the treatment of tumor with radiation mainly depends on the ionization of radiation, which damages the structure of DNA, leads to the damage or destruction of cell ultrastructure, and then leads to the change of cell morphology and tissue reaction. Radiotherapy can also directly cause tumor cell damage, including lethal injury, sublethal injury and potentially lethal injury. Radiotherapy can inhibit tumor vascular regeneration and seal small blood vessels and lymphatic vessels. Notably, radiation can cause an inflammatory reaction in the irradiated site, inducing immune cells to enter the irradiated area, and enhancing the phagocytosis of tumor cells. Besides, radiation-induced bystander effect (RIBE) is predominantly mediated by irradiated tumor cell-released microparticles, which polarized microenvironmental M2 tumor-associated macrophages (M2-TAMs) to M1-TAMs and modulated antitumor interactions between TAMs and

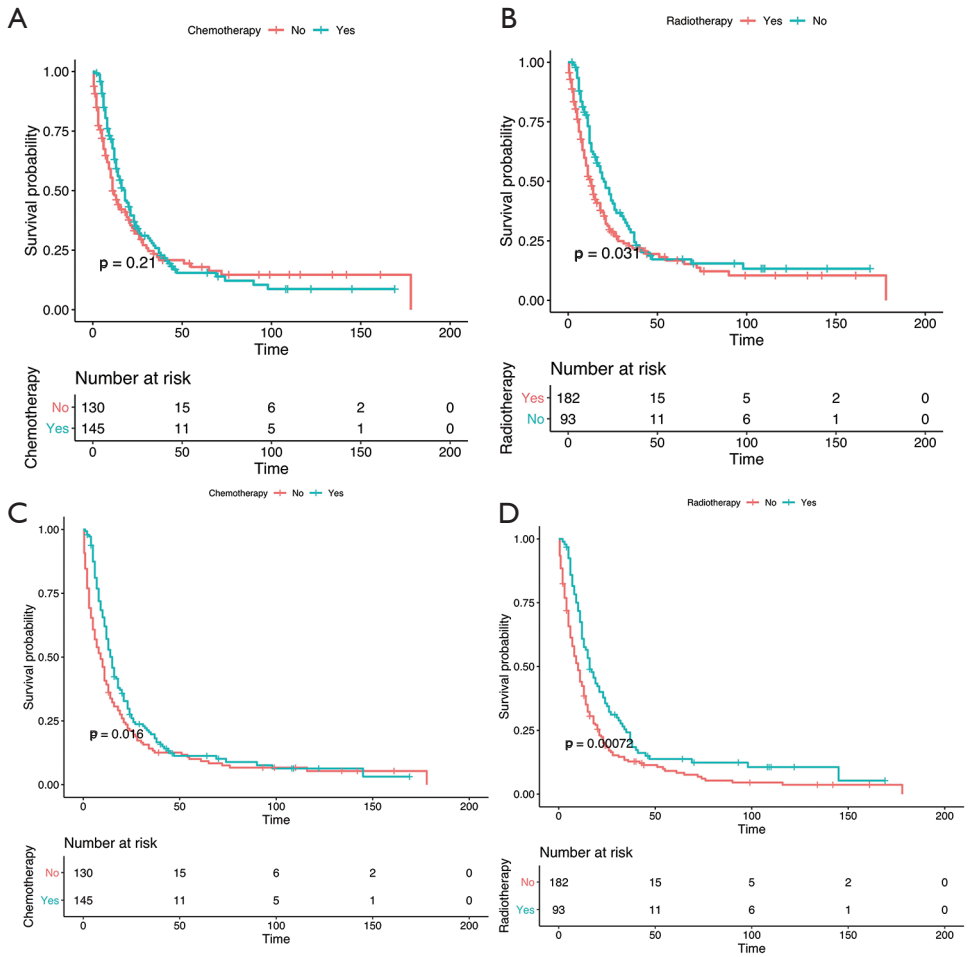

Figure 6 K-M curves were drawn for adjuvant therapy. (A) CSS and (C) OS for patients received chemotherapy; (B) CSS and (D) OS for patients received radiotherapy. K-M, Kaplan-Meier; CSS, cancer-specific survival; OS, overall survival.

tumor cells (44). Thus, the effect of radiation should work continuously, theoretically. Therefore, the inconsistency between 3-year survival and 5-year survival indicated more complicated mechanisms of radiation on GLP.

Since the effect of chemotherapy for GLP is not persistent, there is an urgent need to explore the mechanisms of chemoresistance. First, it is necessary to select the toiled regime for each patient more accurately and to develop novel strategies to overcome chemoresistance (45). In addition, many antitumor drugs are the activation of apoptosis. Thus, a decreased function of pro-apoptotic factors, or the up-regulation of anti-apoptotic factors, might be attributed to the resistance of GC to drugs (5-FU, cisplatin etc.). Thus, hindering the activity of these pathways may increase the sensitivity of GLP to current chemotherapy is to be expected. Further, some research has suggested that pharmacological ascorbate is selectively cytotoxic to GC by a mechanism involving H_2O_2 and redox-active metal ions (46). Hence, pharmacological ascorbate was suggested to be used as an adjuvant with standard-of-care radio-chemotherapies for GC. Lu *et al.* further revealed pharmacological ascorbate inhibits the growth of GC cells and boosts the efficacy of oxaliplatin by redox modulation. In mouse models, the combination of pharmacological ascorbate with genotoxic agents (oxaliplatin, irinotecan etc.), cooperatively suppressed GC growth (47). Thus, pharmacological ascorbate was potential to use as a means of sensitizing GLP to chemoradiotherapy. Other researches indicated that the effect of radiation could also be improved. Since Nicotinamide adenine dinucleotide (NAD+) metabolism is integrally associated with the mechanisms of action of radiation therapy and is changed in many radiation-resistant tumors, NAD+ metabolism was potential to be

Table 5 RMST of CSS for the subgroups of treatments

Treatment	Classification	N	RMST, months								
			1-year			3-year			5-year		
			95% CI	Difference	P value	95% CI	Difference	P value	95% CI	Difference	P value
Chemotherapy	Yes	184	10.4 (9.9–10.8)	1.8 (1.0–2.6)	<0.001	19.6 (17.8–21.5)	3.2 (0.4–6.1)	0.028	23.7 (20.8–26.7)	2.8 (–1.8–7.5)	0.237
	No	158	8.5 (7.8–9.3)			16.4 (14.2–18.7)			20.9 (17.2–24.6)		
Radiotherapy	Yes	117	10.7 (10.3–11.1)	1.9 (1.2–2.6)	<0.001	21.0 (18.8–23.1)	4.3 (1.5–7.1)	<0.001	25.1 (21.6–28.6)	3.9 (–0.7–8.6)	0.100
	No	225	8.9 (8.3–9.4)			16.6 (14.8–18.5)			21.1 (18.1–24.2)		

RMST, restricted mean survival time; CSS, cancer-specific survival; CI, confidence interval.

Table 6 RMST of OS for the subgroups of treatments

Treatment	Classification	N	RMST, months								
			1-year			3-year			5-year		
			95% CI	Difference	P value	95% CI	Difference	P value	95% CI	Difference	P value
Chemotherapy	Yes	184	10.1 (9.6–10.5)	2.7 (1.8–3.5)	<0.001	17.7 (16.1–19.4)	5.0 (2.5–7.5)	<0.001	20.7 (18.2–23.2)	5.3 (1.5–9.1)	0.010
	No	158	7.3 (6.6–8.0)			12.7 (10.9–14.6)			15.4 (12.6–18.2)		
Radiotherapy	Yes	117	10.5 (10.1–11.0)	2.6 (1.9–3.4)	<0.001	19.6 (17.5–21.7)	6.4 (3.8–9.0)	<0.001	23.1 (19.9–26.3)	7.3 (3.4–11.3)	<0.001
	No	225	7.9 (7.3–8.5)			13.2 (11.7–14.8)			15.8 (13.5–18.0)		

RMST, restricted mean survival time; OS, overall survival; CI, confidence interval.

used to enhance radiation sensitivity and improve patient prognosis (48). So, identifying new targets in the NAD+ metabolic network of GLP for therapeutic interventions in combination with radiation therapy was also a potential tactic to explore. Thus, exploring more sensitizing agent is one of the possible strategies to improve the continuous effect of radiotherapy to GLP. More encouragingly, pool analysis recently showed combined radiotherapy with pembrolizumab immunotherapy significantly increased responses and outcomes in patients with metastatic non-small-cell lung cancer (49). This finding gave some inspirations in improving the long term of radiotherapy for GLP.

In our research, the steps of grouping, Cox analysis and nomogram construction & validation have all adopted the current common methods. However, some limits still need to be pointed out. First, the study has inherent flaws in retrospective studies based on public databases like SEER, despite we use relatively strict inclusion criteria to ensure the validity of the results, the bias still can't be ignored. As a result of some pathological or clinical data such as peritoneum metastasis, concrete resection technique and actual chemotherapeutics can't be obtained from the database, further analysis is limited. Besides, GLP is an uncommon type of carcinoma with low prevalence, although we have screened the records of nearly 30 years, the cohort undergoing gastrectomy for GLP was still relatively small, which may influence the stability of the model. Finally, the nomograms constructed in this study still need external validation with other prospective trials.

In conclusions, the models presented in this study might be suitable for clinical use, supporting clinicians in their individualized assessment of expected survival in GLP patients. Notably, chemotherapy and radiotherapy might be beneficial for improving 1- and 3-year OS and CSS, but not the 5-year CSS. This might help guide treatment strategies for patients with GLP and differ from non-GLP patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-264). Dr. YZ reports grants from Southern Medical University, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No formal approval is required as data were collected from a source that was publicly available and did not contain unique patient identifiers. We obtained permission to access research data files of SEER database. Given that these data are de-identified and ethics approval is waived, the study did not require informed consent.

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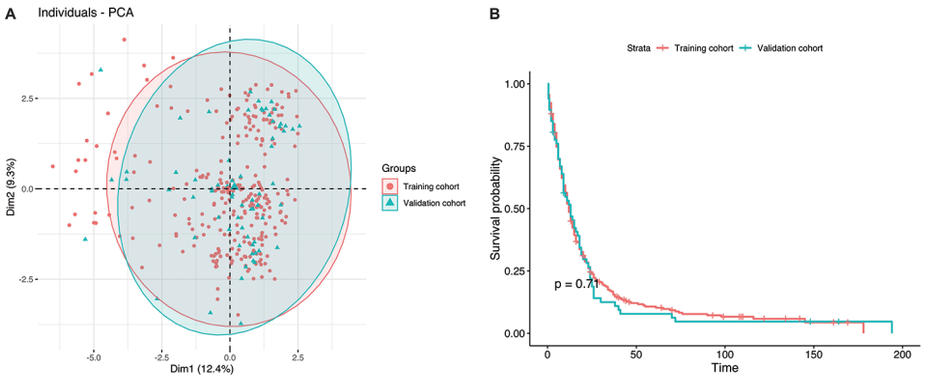

Figure S1 PCA and K-M survival curves indicates that the overall baseline characteristics between cohorts were similar. PCA, principal component analysis; K-M, Kaplan-Meier.

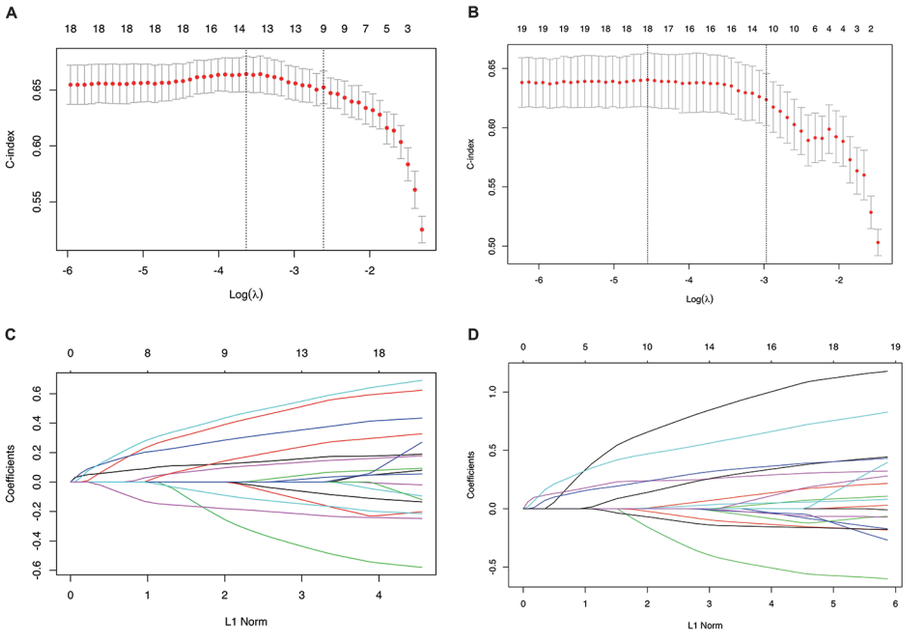

Figure S2 The LASSO regression used to select prognostic factors for OS and CSS. (A) LASSO coefficient for OS; (C) LASSO Cox analysis identified variables for OS; (B) LASSO coefficient profiles of variables for CSS; (D) LASSO Cox analysis identified variables for CSS. LASSO, least absolute shrinkage and selection operator; OS, overall survival; CSS, cancer-specific survival; C-index, concordance index.

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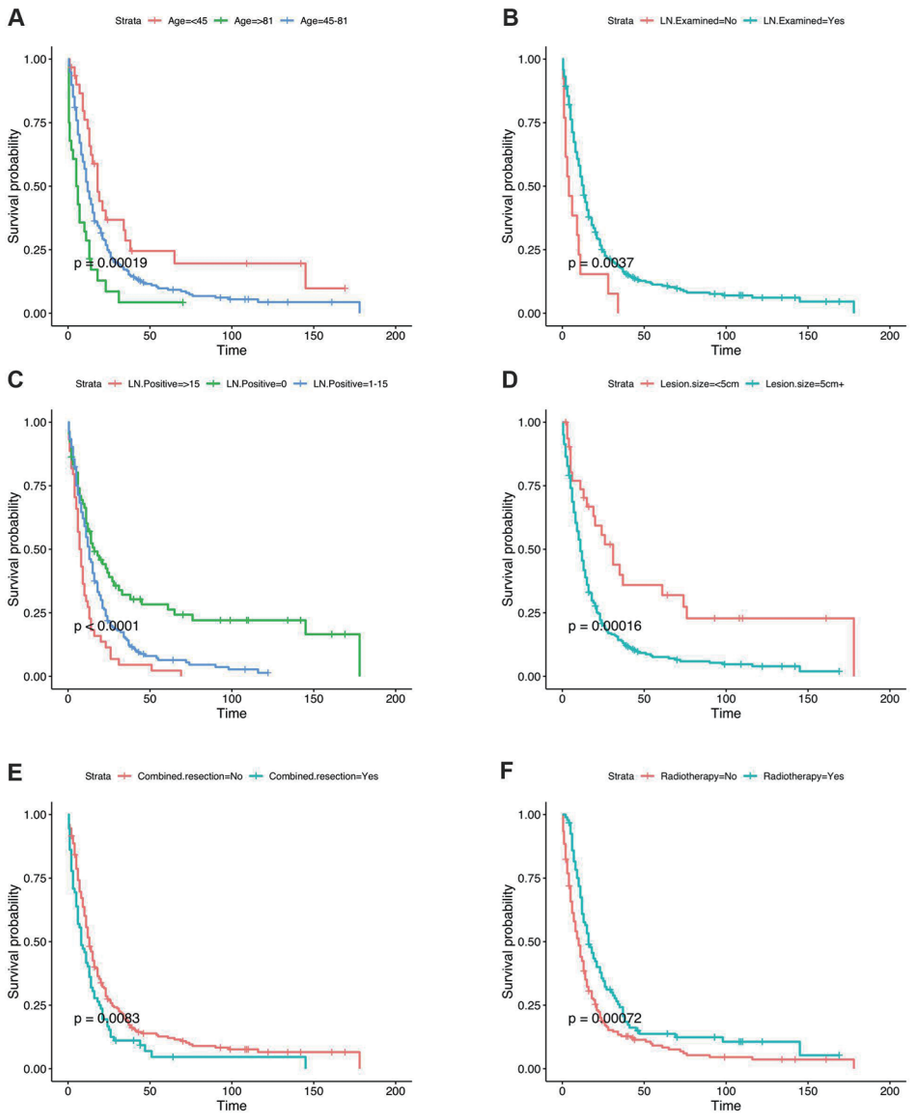

Figure S3 Risk group stratifications within each group for OS model. (A-F) are the OS curves. OS, overall survival; LN, lymph node.

http://dx.doi.org/10.21037/jgo-20-264

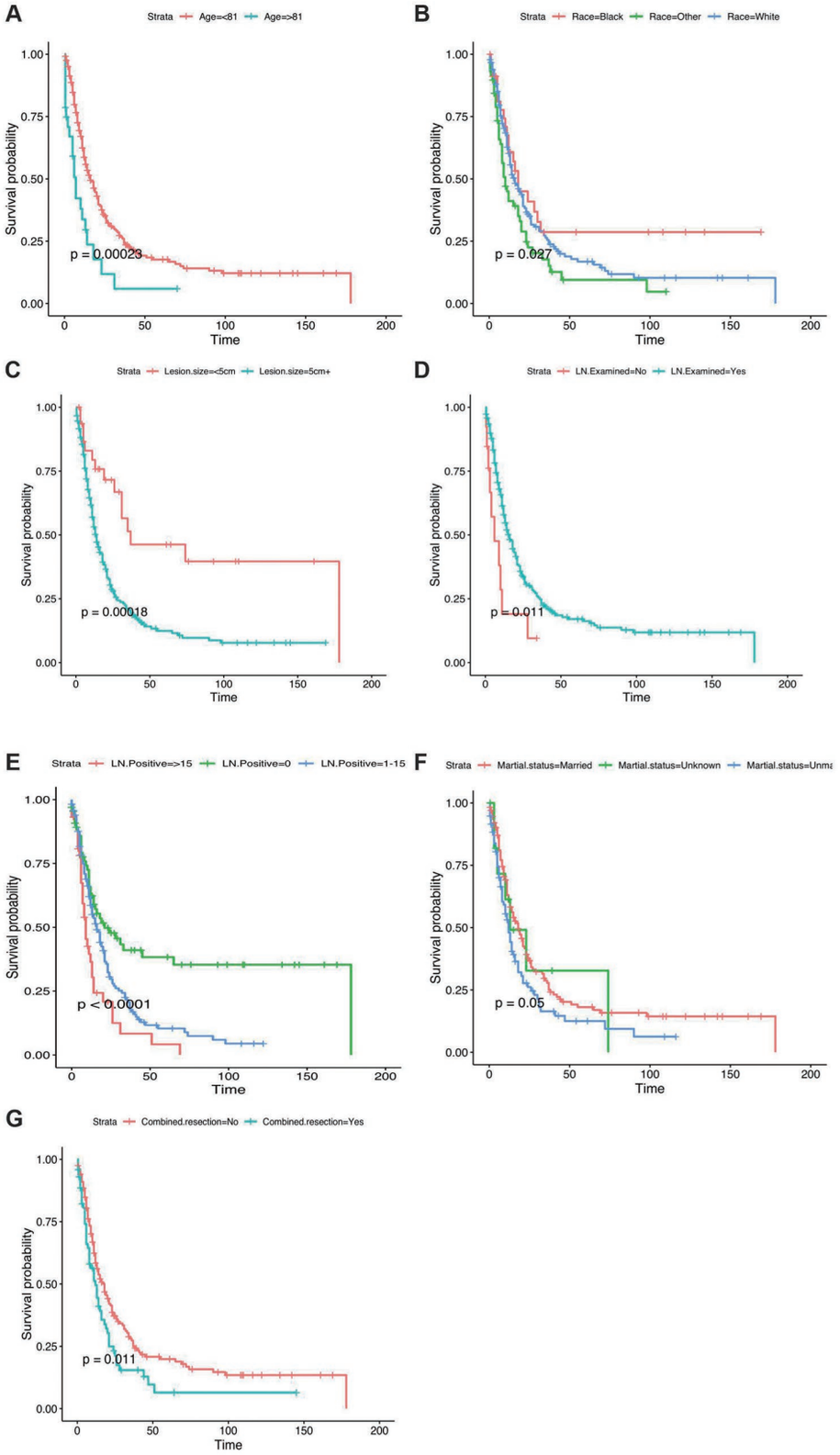

Figure S4 Risk group stratifications within each group for CSS model. (A-G) are the CSS curves. CSS, cancer-specific survival; LN, lymph node.

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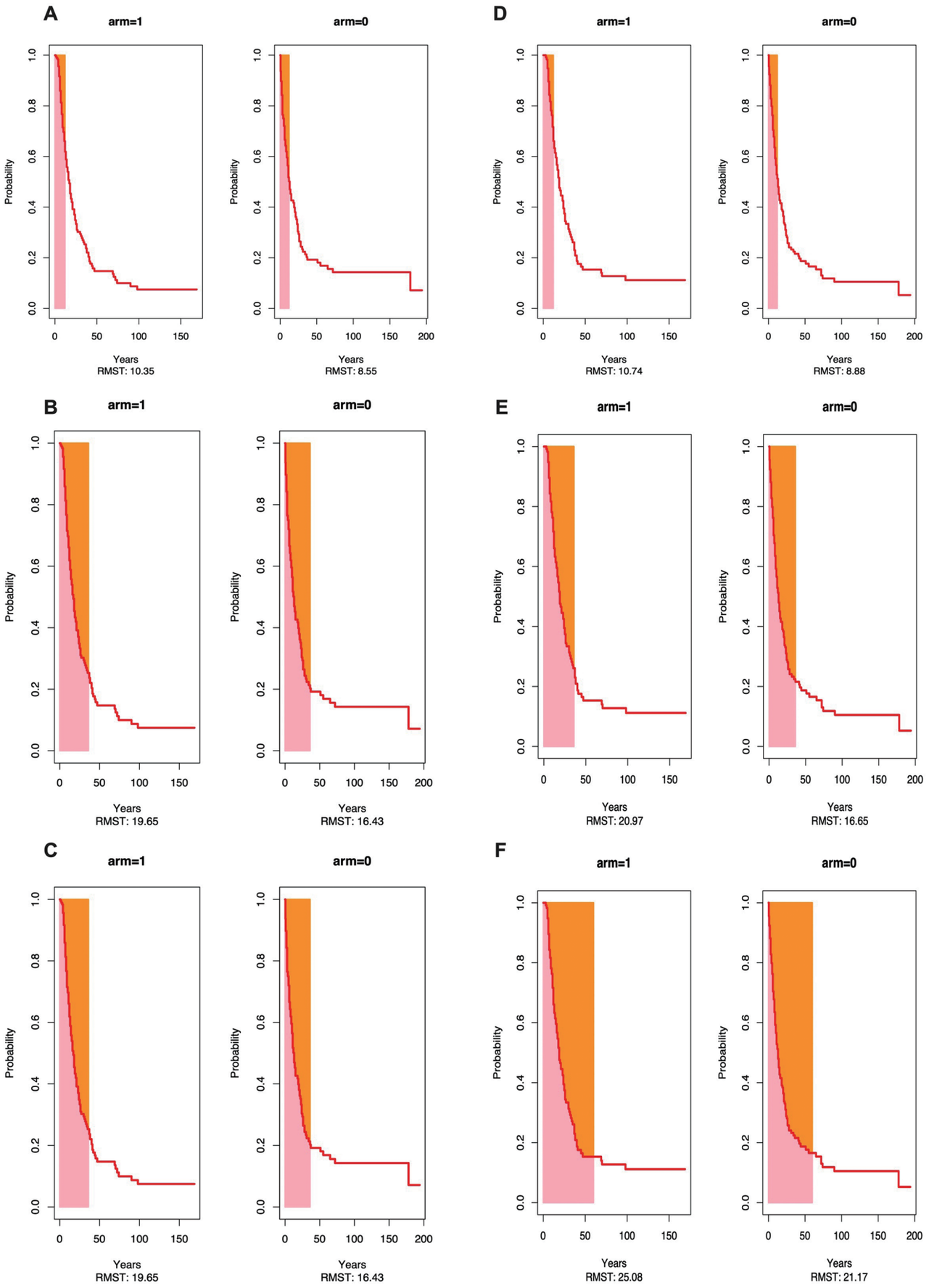

Figure S5 TRMST analysis was used to analyze the actual therapeutical effect of CT (A-C) and RT (D-F). CSS was used as the endpoint of the study. Arm =1 represents the RT or CT group, while arm =0 represents the non-RT or non-CT group. (A,D) represents 1-year CSS, (B,E) represents 3-year CSS, (C,F) represents 5-year CSS. RMST, restrict mean survival time; CT, chemotherapy; RT, radiotherapy; CSS, cancer-specific survival.

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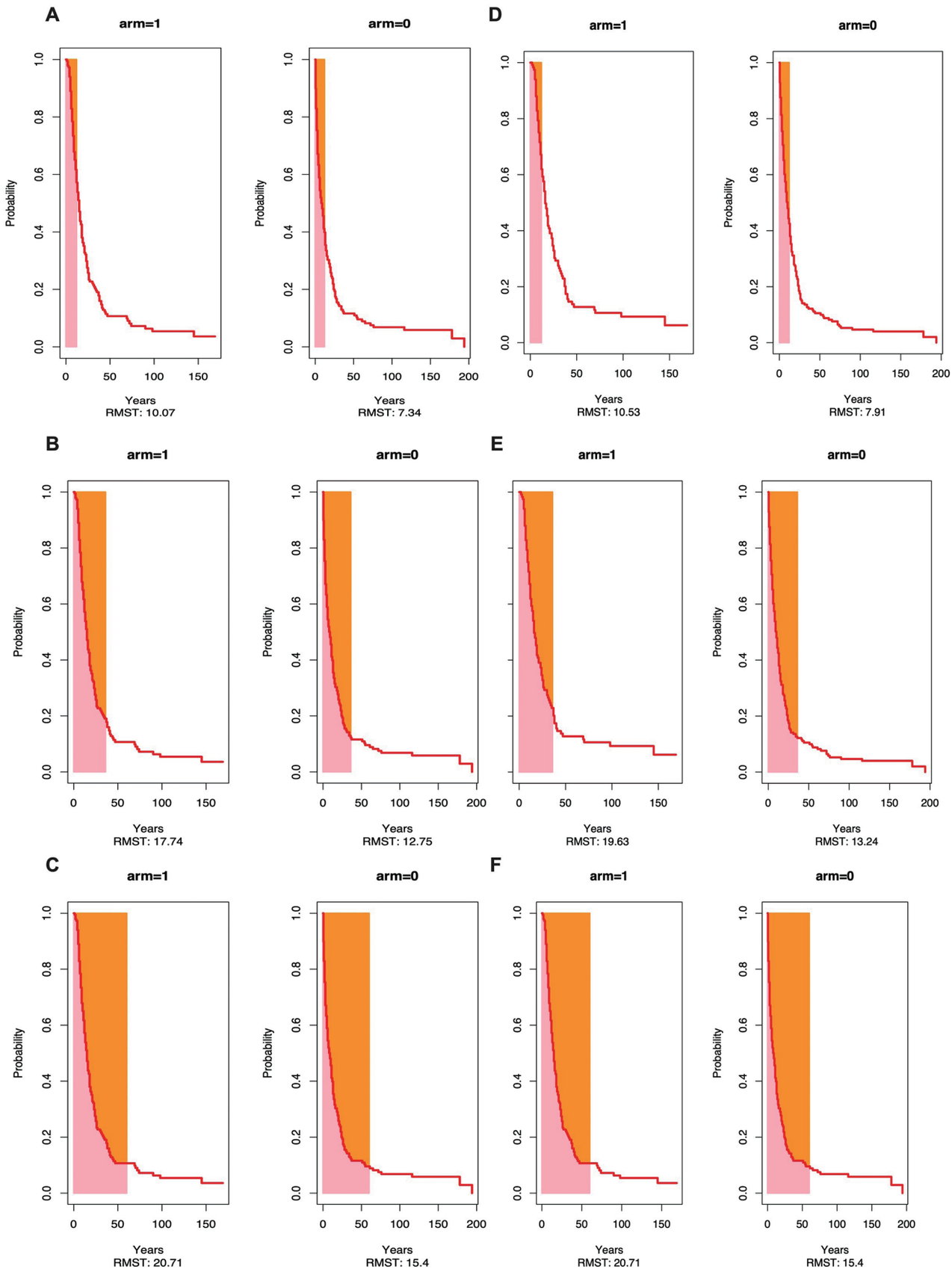

Figure S6 RMST analysis was used to analyze the actual therapeutical effect of CT (A-C) and RT (D-F). OS was used as the endpoint of the study. Arm =1 represents the RT or CT group, while arm =0 represents the non-RT or non-CT group. (A,D) represents 1-year OS, (B,E) represents 3-year OS, (C,F) represents 5-year OS. RMST, restrict mean survival time; CT, chemotherapy; RT, radiotherapy; OS, overall survival.

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