Development and validation of a prognostic model based on SEER data for patients with Combined small-cell lung cancer

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Article

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Abstract

Background: To analyze the prognostic factors of combined small cell lung cancer (CSCLC) and construct a nomogram model for CSCLC.

Methods:

A total of 978 patients diagnosed with CSCLC from 2010 to 2015 were collected based on the SEER database. According to the ratio of 7:3, the patients were divided into the modeling group and the testing group. Univariate and multivariate Cox regression analyses were performed on the patients in the modeling group to analyze the independent factors affecting the prognosis of CSCLC patients and construct a nomogram prediction model, which was verified by the C-index and calibration curve in the training cohort and the validation cohort, respectively.

Results:

Univariate and multivariate Cox regression analysis showed that N stage, M stage, surgery, chemotherapy, radiotherapy, age, brain metastases, lung metastases, liver metastases, bone metastases, and tumor size were independent risk factors affecting the prognosis of CSCLC patients (P<0.05). A nomogram prediction model was constructed based on the above 10 risk factors through visual analysis, and the C-index was 0.753 (95%CI: 0.727~0.750). The calibration curves showed good agreement between the 1 -, 2 -, and 3-year predicted and actual survival rates of the prediction model constructed in this study. The AUC of the 1-, 2-, and 3-year prediction models was 0.813, 0.814, and 0.802, respectively. DCA showed that the nomogram model had more clinical application value in predicting survival prognosis than TNM staging. Finally, according to the total score of the nomogram survival prediction model, all the included cases were divided into low-risk, intermediate-risk, and high-risk strata and these three survival curves of each risk stratification showed significant survival differences (p< 0.05).

Conclusions:

The nomogram prediction model constructed in this study has higher accuracy and clinical application value than the traditional TNM staging. It can predict the 1 -, 2 - and 3-year OS of patients individually and provide a new tool for clinicians to evaluate the survival prognosis of CSCLC. The risk stratification system established by this model can identify high-risk patients more quickly, and make follow-up plans and subsequent treatment plans more targeted.

Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality worldwide[1]. Small cell lung cancer (SCLC) accounts for 15%-20% of all lung cancers, and its biological behavior is significantly different from other pathological types of lung cancer[2]. Its biological behavior is obviously different from other pathological types of lung cancer[3]. The mixture of components is called compound

small cell lung cancer. The components of NSCLC can be squamous cell carcinoma, adenocarcinoma, large cell neuroendocrine tumor, even spindle cell carcinoma, giant cell carcinoma, etc. Mixed components can be one or more. At present, mixed squamous cell carcinoma is the most common[4-6]. So far, there is still a lack of large-sample prospective randomized controlled clinical research data on the treatment of combined SCLC, and most of them are small-sample retrospective analyses and case reports. The American Joint Committee on Cancer (AJCC) TNM staging system is the most widely used to predict the prognosis of cancer patients by assessing tumor size, lymph node, and distant metastasis. However, the TNM staging system still has some limitations, so the establishment of a new prediction system combining a variety of clinicopathological factors can further improve the accuracy of evaluating the prognosis of CSCLC.

Nomogram is a combination of multiple factors to quantify the probability of the occurrence of clinical events, which transforms the complex regression equation into a simple and visual graphical model, making the results of the prediction model more readable and more valuable[7]. In recent years, it has been widely accepted in the field of medical research. However, there is no relevant prediction model to evaluate the survival of CSCLC. The aim of this study is to construct and validate a nomogram prediction model that can be used for individualized risk assessment of CSCLC.

Methods

This study was implemented following good practice guidelines and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Baoding Science and Technology Planning Project, Project No. 2241ZF127. An informed consent was obtained from all the participants.

Patient selection

Data were extracted from the SEER database with the use of SEER*Stat software, version 8.4. The database has been improved since 2010, and the relevant information on tumor metastasis has been extracted through the inclusion and exclusion criteria 978 cases diagnosed with CSCLC from 2010 to 2015 in SEER*Stat software (version 8.3.6) as shown in Fig.1. The data collected included primary site, TNM stage, surgery, chemotherapy, radiotherapy, age, brain metastases, lung metastases, liver metastases, bone metastases, grade, and tumor size.

Inclusion and exclusion criteria

Inclusion criteria: Pathological diagnosis of CSCLC; Complete clinical information; Age ≥18 years old. Exclusion criteria: missing or unclear clinical/pathological information; Non-first primary lung cancer.

Research Methods

The clinical data of the patients were collected. Including gender, age (24-66 years, 67-77 years,78+ years), race (American Indian/Alaska Native, Asian or Pacific Islander, Black, and White), the tumor

location of the primary site (upper lobe, middle lobe, lower lobe and other), laterality (left, other, and right), grade of differentiation (, , ,), T stage (T1, T2, T3, T4, and TX), N stage (N1, N2, N3, and NX), M stage (M0, M1), chemotherapy (No and Yes), radiotherapy (No and Yes), surgery (No and Yes), brain metastases (No and Yes), bone metastases (No and Yes), liver metastases (No and Yes), lung metastases (No and Yes), and the tumor size(≤30 mm, > 31-50 mm, > 51-70 mm, > 70 mm and unknown). Firstly, univariate and multivariate cox regression analyses were performed to construct a model and draw a nomogram based on independent risk factors, and the nomogram was verified to evaluate the accuracy and sensitivity of the model.

Statistical analysis

SPSS 22.0 and R 3.6.2 software were used for analysis. The count data were expressed as a percentage (%). The survival rate and median survival time were calculated by the Kaplan-Meier method and the survival curve was drawn. SPSS 22.0 software was used for univariate and multivariate Cox regression analysis of variables. Based on the results of multivariate regression, the rms package in R3.6.2 software was used to draw a nomogram and calculate the consistency index (C-index). The calibration chart and receiver operating characteristic (ROC) curve were drawn to evaluate the predictive ability of the model. The C-index ranged from 0.50 to 1.00, with higher values indicating better discrimination of the model. The area under the ROC curve (AUC) ranged from 0.50 to 1.00, and the higher the AUC value, the better the predictive ability of the model. $P<0.05$ was considered statistically significant. The clinical application value of the nomogram was evaluated by decision curve analysis (DCA).

Results

Baseline characteristics

A total of 978 patients were finally screened for inclusion and exclusion criteria in this study. The detailed clinicopathological features of all cases were shown in Table 1. First, the overall data were randomly divided into a training cohort and validation cohort at a ratio of 7:3, and the caret package in R software was used for randomization. The data were sorted according to the data processing method described in the methods. A total of 16 indicators including sex, age, race, T stage, N stage, M stage, radiotherapy, chemotherapy, surgery, primary site, laterality, brain metastases, bone metastases, liver metastases, lung metastases, and tumor size were included to analyze the prognosis of CSCLC patients.

Table 1 Demographics and characteristics of patients in Training and Validation cohorts

Characteristics	Whole Patients		Training cohort		Validation cohort	
	n=978	%	n=686	%	n=292	%
Sex						
Female	460	46.2	318	46.4	134	45.90
Male	536	53.8	368	53.6	158	54.10
Race						
American Indian/Alaska Native	11	1.1	9	1.3	2	0.7
Asian or Pacific Islander	42	4.2	29	4.2	12	4.1
Black	110	11	75	10.9	33	11.3
White	833	83.6	573	83.5	245	83.9
T stage						
T1	134	13.5	97	14.1	35	12
T2	162	16.3	101	14.7	55	18.8
T3	124	12.4	73	10.6	48	16.4
T4	131	13.2	83	12.1	45	15.4
TX	445	44.7	332	48.4	109	37.3
N stage						
N0	207	20.8	145	21.1	57	19.5
N1	56	5.6	40	5.8	14	4.8
N2	218	21.9	125	18.2	88	30.1
N3	89	8.9	59	8.6	28	9.6
NX	426	42.8	317	46.2	105	36
Radiotherapy						
No	527	52.9	361	52.6	154	52.7
Yes	469	47.1	325	47.4	138	47.3
Chemotherapy						
No/Unknown	332	33.3	218	31.8	104	35.6
Yes	664	66.7	468	68.2	188	64.4

Surgery						
No	728	73.1	500	72.9	210	71.9
Yes	268	26.9	186	27.1	82	28.1
Grade						
I	12	1.2	6	0.9	6	2.1
II	34	3.4	27	3.9	7	2.4
III	246	24.7	167	24.3	74	25.3
IV	117	11.7	83	12.1	33	11.3
Unknown	575	58.8	403	58.7	172	58.9
Age						
24-66 years	409	41.1	281	41	120	41.1
67-77 years	407	40.9	286	41.7	116	39.7
78+ years	180	18.1	119	17.3	56	19.2
Tumor size						
0-30 mm	222	22.3	153	22.3	67	22.90
31-50 mm	128	12.9	79	11.5	45	15.40
51-70 mm	60	6	35	5.1	22	7.50
70+ mm	87	8.7	56	8.2	30	10.30
Unknown	499	50.1	363	52.9	128	43.80
M stage						
M0	319	32	215	31.3	103	35.3
M1	269	27	161	23.5	91	31.2
MX	408	41	310	45.2	98	33.6
Primary Site						
Upper lobe, lung	543	54.5	54.4	54.4	162	55.5
Middle lobe, lung	35	3.5	3.8	3.8	9	3.1
Lower lobe, lung	266	26.7	27	27	76	26
Other	152	15.3	14.9	14.9	45	15.4
Laterality						

Left	412	41.4	287	41.8	114	39
Other	39	3.9	29	4.2	8	2.7
Right	545	54.7	370	53.9	170	58.2
Lung metastases						
No	856	87.5	601	87.6	255	87.3
Yes	122	12.5	85	12.4	37	12.7
Liver metastases						
No	833	85.2	581	84.7	252	86.3
Yes	145	14.8	105	15.3	40	13.7
Brain metastases						
No	853	87.2	604	88	249	85.3
Yes	125	12.8	82	12	43	14.7
Bone metastases						
No	831	85	588	85.7	243	83.2
Yes	147	15	98	14.3	49	16.8

Independent predictors in the study population

Univariate analysis showed that primary site, T stage, N stage, M stage, surgery, chemotherapy, radiotherapy, age, brain metastases, lung metastases, liver metastases, bone metastases, grade, and tumor size were important factors affecting OS. In univariate analysis, $p<0.05$ were included in the multivariate analysis. The results of univariate and multivariate analysis of the modeling group showed that N stage, M stage, surgery, chemotherapy, radiotherapy, age, brain metastases, lung metastases, liver metastases, bone metastases, and tumor size were independent risk factors for poor prognosis in CSCLC, as shown in Table 2.

Table 2 Univariate and multivariate Cox analysis of prognostic factors

Variable		Univariate analysis				Multivariate analysis			
	n	HR (95% CI)			p-value	HR (95% CI)			p-value
Sex					0.183				1.054
female	318	Reference							
male	368	1.126	0.945	1.342		1.054	0.878	1.265	
Race									
America	9	Reference			0.338				
Asian o	29	1.559	0.634	3.832	0.333				
Black	75	0.998	0.429	2.32	0.996				
White	573	1.167	0.521	2.614	0.707				
Site					0.001				
Lower l	185	Reference				Reference			0.575
Middle	26	0.896	0.566	1.419	0.64				
OTHER	102	1.536	1.168	2.019	0.002	0.884	0.549	1.422	0.611
Upper l	373	0.944	0.768	1.16	0.584	1.147	0.854	1.54	0.362
Laterality					0.182	0.964	0.775	1.199	0.741
Left -	287								
OTHER	29	1.399	0.91	2.152	0.126				
Right -	370	0.942	0.787	1.128	0.517				
T stage					<0.001				
T1	97	Reference							
T2	101	1.403	1.03	1.91	0.032				
T3	73	1.869	1.344	2.6	<0.001				
T4	83	2.377	1.731	3.265	<0.001				
TX	332	1.455	1.113	1.903	0.006				
N stage					<0.001			<0.001	
N0	145	Reference				Reference			
N1	40	1.535	1.055	2.232	0.025	1.786	1.2	2.658	0.004
N2	125	2.341	1.798	3.048	<0.001	1.771	1.319	2.378	<0.001

N3	59	2.161	1.563	2.989	<0.001	1.185	0.814	1.725	0.376
NX	317	1.518	1.189	1.939	0.001	3.672	1.614	8.354	0.002
M					<0.001				<0.001
M0	215	Reference				Reference			
M1	161	3.163	2.523	3.966	<0.001	1.53	1.131	2.07	0.006
MX	310	1.449	1.163	1.804	0.001	0.341	0.144	0.809	0.015
Surgery					<0.001				<0.001
No	500	Reference							
Yes	186	0.35	0.281	0.436		0.412	0.313	0.542	
CT					<0.001				<0.001
No	218	Reference							
Yes	468	0.646	0.538	0.777		0.544	0.44	0.671	
RT					0.017				<0.001
No	361	Reference							
Yes	325	0.808	0.678	0.962		0.646	0.526	0.793	
Age					<0.001				0.002
24-66	281	Reference							
67-77	286	1.141	0.94	1.387	0.183	1.084	0.886	1.325	0.433
78+	119	1.678	1.319	2.136	<0.001	1.61	1.229	2.109	0.001
Grade					0.224				
I	6	Reference							
II	27	0.518	0.209	1.285	0.156				
III	167	0.623	0.275	1.413	0.258				
IV	83	0.621	0.269	1.435	0.265				
Unknown	403	0.736	0.328	1.655	0.459				
T size					<0.001				
0-30	153	Reference							
31-50	79	1.419	1.054	1.911	0.021				
51-70	35	2.232	1.516	3.286	<0.001				

70+	56	2.289	1.654	3.168	<0.001				
Unknown	363	1.477	1.179	1.849	0.001				
LUNG					<0.001				0.182
No	601								
Yes	85	2.428	1.887	3.124		1.212	0.914	1.608	
LIVER									0.005
No	581	Reference			<0.001				
Yes	105	2.805	2.228	3.531		1.466	1.12	1.918	
BRAIN					<0.001				0.001
No	604	Reference							
Yes	82	2.151	1.658	2.792		1.661	1.24	2.225	
Bone					<0.001				0.004
No	588	Reference							
Yes	98	2.473	1.95	3.136		1.492	1.14	1.952	

Prognostic nomogram building and validation

According to the impact of each variable on the prognosis in the multivariate analysis, the nomogram assigns a value to each variable and finally adds the score to visualize the prognosis of the patient. The results of multivariate analysis of the training cohort showed N stage, M stage, surgery, chemotherapy, radiotherapy, age, brain metastases, lung metastases, liver metastases, bone metastases, and tumor size are independent prognostic factors for CSCLC patients. The above 10 variables were used to construct a nomogram survival prediction model, and the 1 -, 2 -, and 3-year overall survival of CSCLC patients were predicted by drawing the nomogram, as shown in Fig.2.

This nomogram prediction model was constructed based on the above 10 risk factors, and the C-index was 0.753 (95%CI: 0.727~0.750), which was significantly better than the C-index (0.655 (95% CI: 0.627–0.656) of the AJCC staging system. In the validation cohort, the C-index of this prediction model and the C-index of the AJCC analysis system were 0.739 (95%CI: 0.700~0.736) and 0.637 (95% CI: 0.608–0.653), respectively. The consistency was evaluated using the calibration curve. The Bootstrap method was used in the training cohort and the validation cohort, and 1000 times repeated sampling was used for verification, and the results are shown in Fig.3A-F. The 1-, 2-, and 3-year OS predicted by the nomogram model were consistent with the actual 1-, 2-, and 3-year OS of the patients, indicating that the nomogram prediction model had a good consistency.

The ROC curve was used to compare the difference in discrimination accuracy between the established nomogram and the TNM staging system. We plotted the ROC curves of the nomogram and TNM staging for predicting 1 -, 2 -, and 3-year OS in the validation cohort, respectively, and calculated the AUC values. The results showed that the nomogram established in this study had higher predictive efficacy than the TNM staging system in predicting the 1 -, 2 -, and 3-year OS, as shown in Fig.4A-F.

ROC curve analysis was used to evaluate the efficiency of the nomogram model in predicting the prognosis of CSCLC patients. The area under the curve of the 1-year, 2-year, and 3-year prediction models was 0.813, 0.814, and 0.802, respectively, indicating that the nomogram model had good prediction accuracy, as shown in Fig.4A-F.

Differences in the Nomogram and the 7th AJCC TNM Stage System

Decision curve analysis (DCA) is a way to evaluate the clinical value of the nomogram prediction model, and its evaluation effect is better than AUC and more accurate. As shown in Fig.5, the DCA curve of the nomogram prediction model is better than that of the TNM staging, indicating that the nomogram prediction model has a certain clinical application value, and its prediction effect is better than that of the TNM staging.

Risk Stratification Model and Survival analysis.

According to the score of each independent predictor in the nomogram model, the total score of each patient was calculated by adding each score. The X-tile software was used to intercept the best cut-off value, and the CSCLC patients were stratified according to the risk size: low-risk group (71-185), intermediate-risk group (186-260), and high-risk group (261-368) (Fig.6). The log-rank method was used to test the differences between groups to evaluate the accuracy of risk stratification based on the nomogram prediction model score.

Discussion

In 2015, the World Health Organization (WHO) classified small-cell lung cancer into two types, including SCLC and combined SCLC[8, 9]. If the presence of any NSCLC component in SCLC can be classified as CSCLC, there is no requirement for the proportion of NSCLC. At present, the recognized tool for evaluating the prognosis of CSCLC is the AJCC TNM staging system recommended by the Union for International Cancer Control[10] and the older Veterans Administration (VA) scheme[11]. The TNM staging system mainly depends on surgery to verify its accuracy. However, most CSCLCs have lost the opportunity for surgery at the time of diagnosis and can only receive radiotherapy and chemotherapy. The AJCC staging system cannot accurately evaluate the prognosis of CSCLC. Therefore, we developed a survival prognostic model for CSCLC in the above context.

The NCCN guideline expert group recommends that the treatment patterns of CSCLC and SCLC are basically the same according to the stage. For the treatment of combined small cell lung cancer, there is

still a lack of large sample prospective randomized controlled clinical trial data, and most of them are small sample retrospective analysis and case reports. Therefore, the current guidelines all classify compound small cell lung cancer as small cell lung cancer, and adopt the same treatment mode, but lack of more individualized and specific treatment strategies. Surgical resection can be considered for limited stage patients with no hilar and mediastinal lymph node metastasis after systematic staging examination, and the maximum diameter of the tumor is less than 5cm, and the adjacent organs are not invaded (T1-2N0M0, I-IIA). Lobectomy plus hilar and mediastinal lymph node dissection is the first choice for surgery. Surgery not only contributes to the diagnosis of CSCLC but also has a more significant benefit from surgical resection compared with pure SCLC[6, 12, 13]. The results of this study also found that surgery can improve the survival of CSCLC, which is consistent with the conclusions of previously published studies. For LD patients with active status according to the Eastern Cooperative Oncology Group (ECOG) criteria, higher stage than T1-2N0, and a PS score of 0-2, the main treatment was chemotherapy plus radiotherapy (either simultaneously or sequential). For LD patients with PS score of 3-4, chemotherapy and symptomatic supportive therapy were the main treatments[14, 15].

For ED patients, platinum-based combination chemotherapy regimens are used at the beginning of treatment for ES-SCLC patients, and EP regimen is the most commonly used combination chemotherapy regimen. The NCCN SCLC Panel recommends combined chemotherapy and immunotherapy as the preferred treatment for extensive-stage SCLC. For patients with extensive-stage SCLC and brain metastases, systemic therapy can be administered either before or after brain radiotherapy, depending on the presence or absence of neurologic symptoms. If systemic therapy was given first, radiation to the brain was administered after completion of systemic therapy. Although information on immunotherapy was not available, the results of this study show that both radiotherapy and chemotherapy can model-improve survival in patients with CSCLC, which is consistent with the results of previously published studies[16-18].

According to the univariate and multivariate cox proportional hazards regression model analysis, the independent risk factors affecting the survival and prognosis of CSCLC were obtained. Most of the factors included in this study were highly consistent with the results of previous studies. The best cut-off value obtained by X-tile software analysis was 63 years old and 80 years old, so the age was divided into three groups. We speculated that elderly patients with more comorbidities and intolerance to radical treatment might be the reasons for low survival rate. In addition, tumor size and distant organ metastasis are also independent risk factors for CSCLC, which is consistent with the conclusions of previous studies.

In the validation group, the accuracy of the prediction model in this study was verified by the calibration curve, which was highly consistent with the actual survival. In addition, the C-index, area under the ROC curve (AUC) and decision curve (DCA) of the prediction model in this study were better than those of the TNM staging system. In addition, this study attempts to predict the total score through the nomogram prediction model, and the risk is divided into three groups of low, medium and high according to the score. Analysis shows the accuracy of risk stratification of the prediction model, which can effectively

identify between high-risk layers and provide decision-making basis for the survival outcome of low-risk patients and different treatment options for patients.

This study had several limitations. This study is a retrospective study based on the SEER database, and the selection of its data is inevitably subject to selection bias There are some limitations within the study. In addition, the SEER data were collected on patients located in the United States, Regional differences in the model cannot be excluded, so more data from institutional centers in different countries are needed to adjust the model.

Conclusion

The results indicated that age, tumor size, M stage, N stage, chemotherapy, radiotherapy, surgery, and metastasis of bone, brain, and liver are independent variables for OS and prognosis of CSCLC. Secondly, we developed a new survival prediction model with high accuracy, and its prediction performance was significantly better compared with that of the AJCC stage system. It can more accurately and individually predict the OS of patients and assist clinicians in formulating better individual treatment strategies.

Declarations

Data availability

The dataset from SEER database analyzed during the current study are available in the SEER dataset repository (https://seer.cancer.gov/).

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Figures

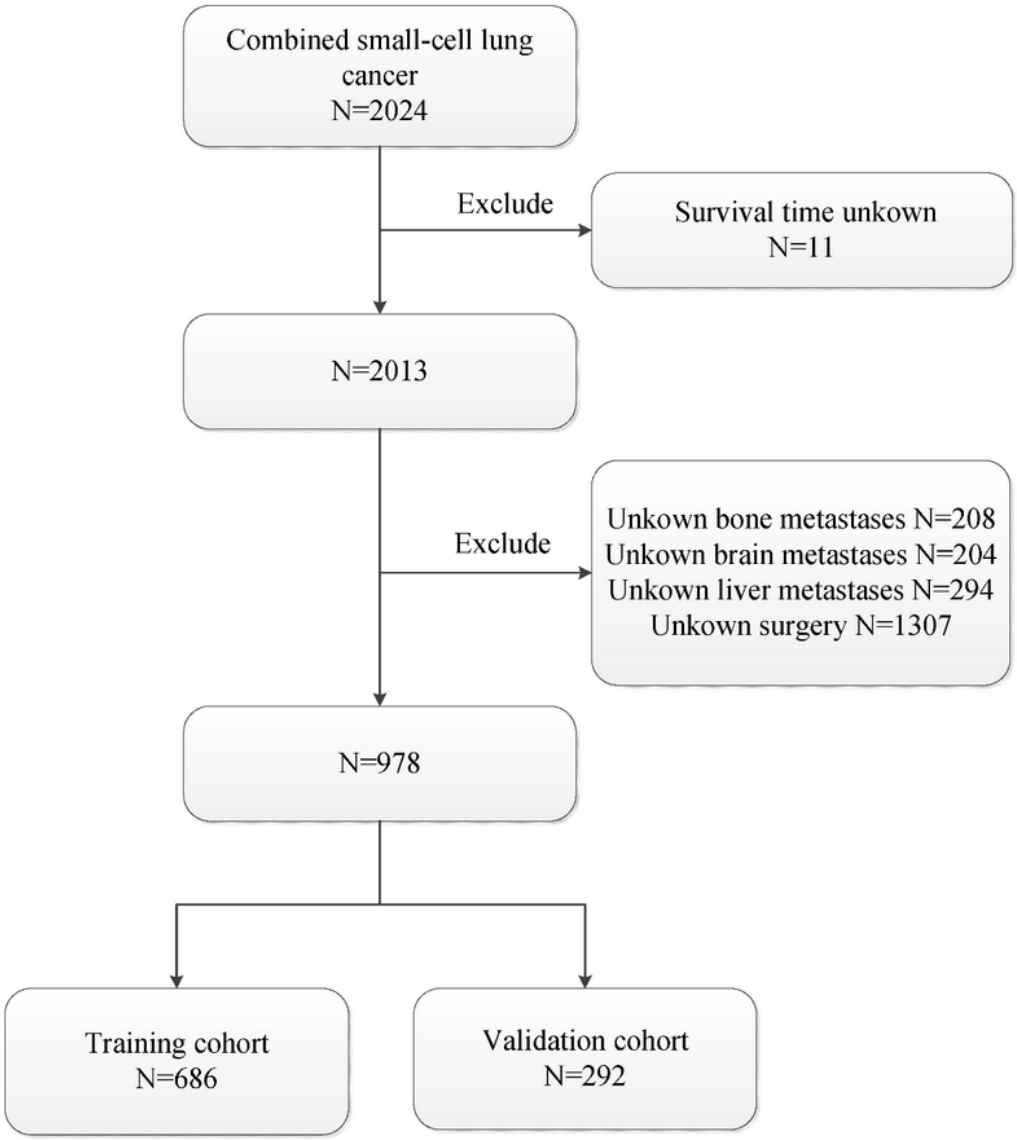

Figure 1

Flow diagram of selection process.

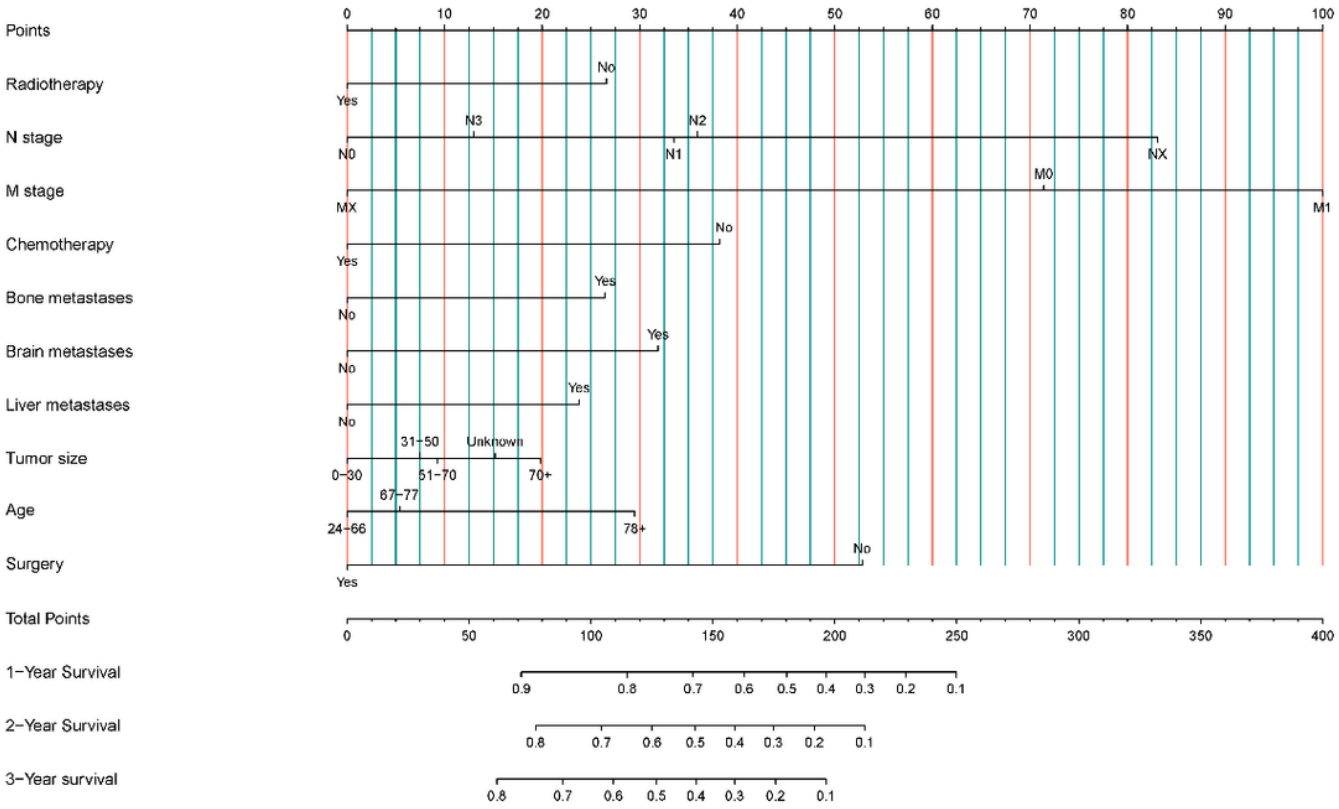

Figure 2

Development of a prognostic stratification nomogram and validation of the proposed nomogram.

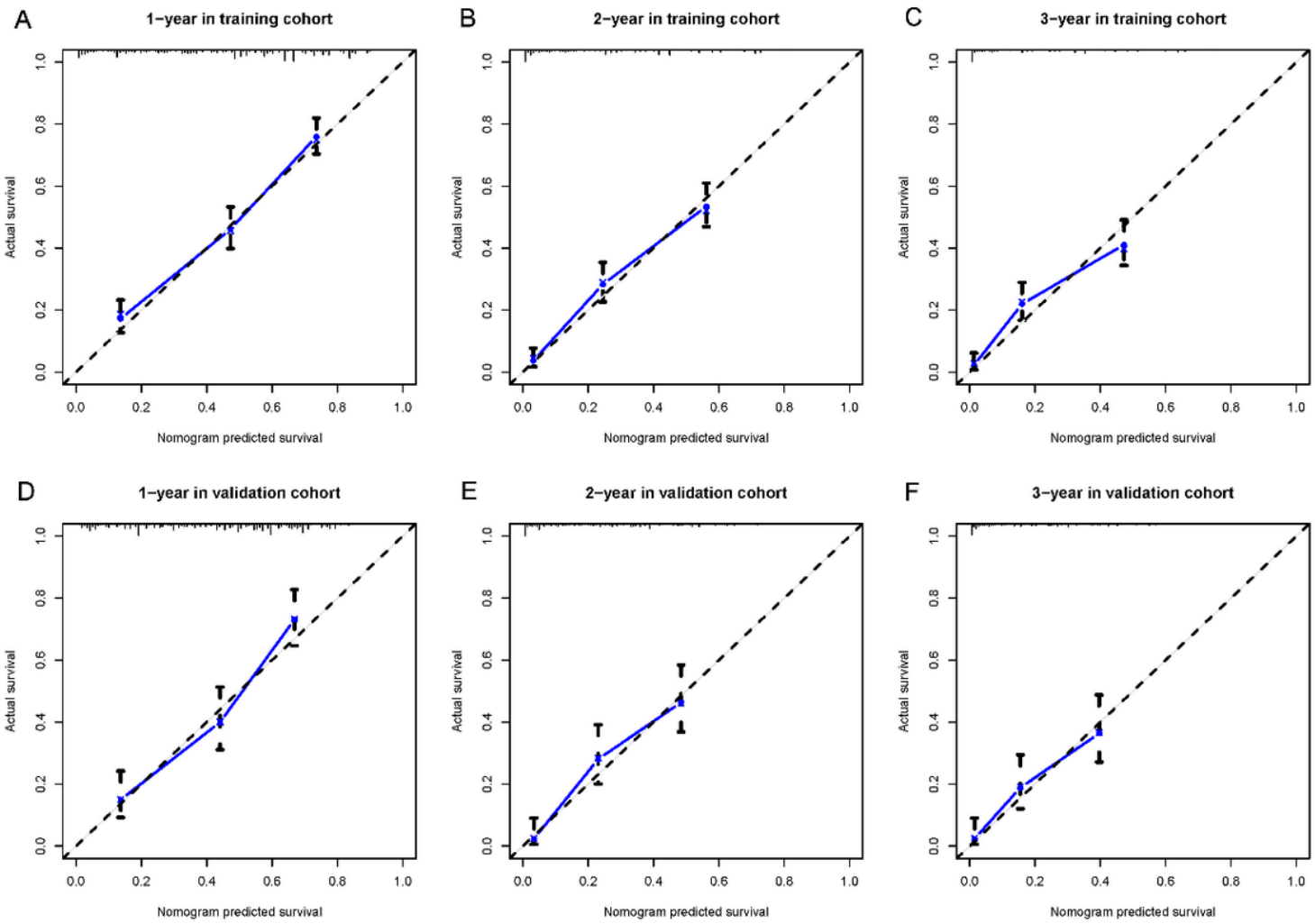

Figure 3

The receiver operating characteristic (ROC) curve for nomogram in the training cohort (A-C) and validation cohort (D-F) at 1-year, 2-year, and 3-year, respectively.

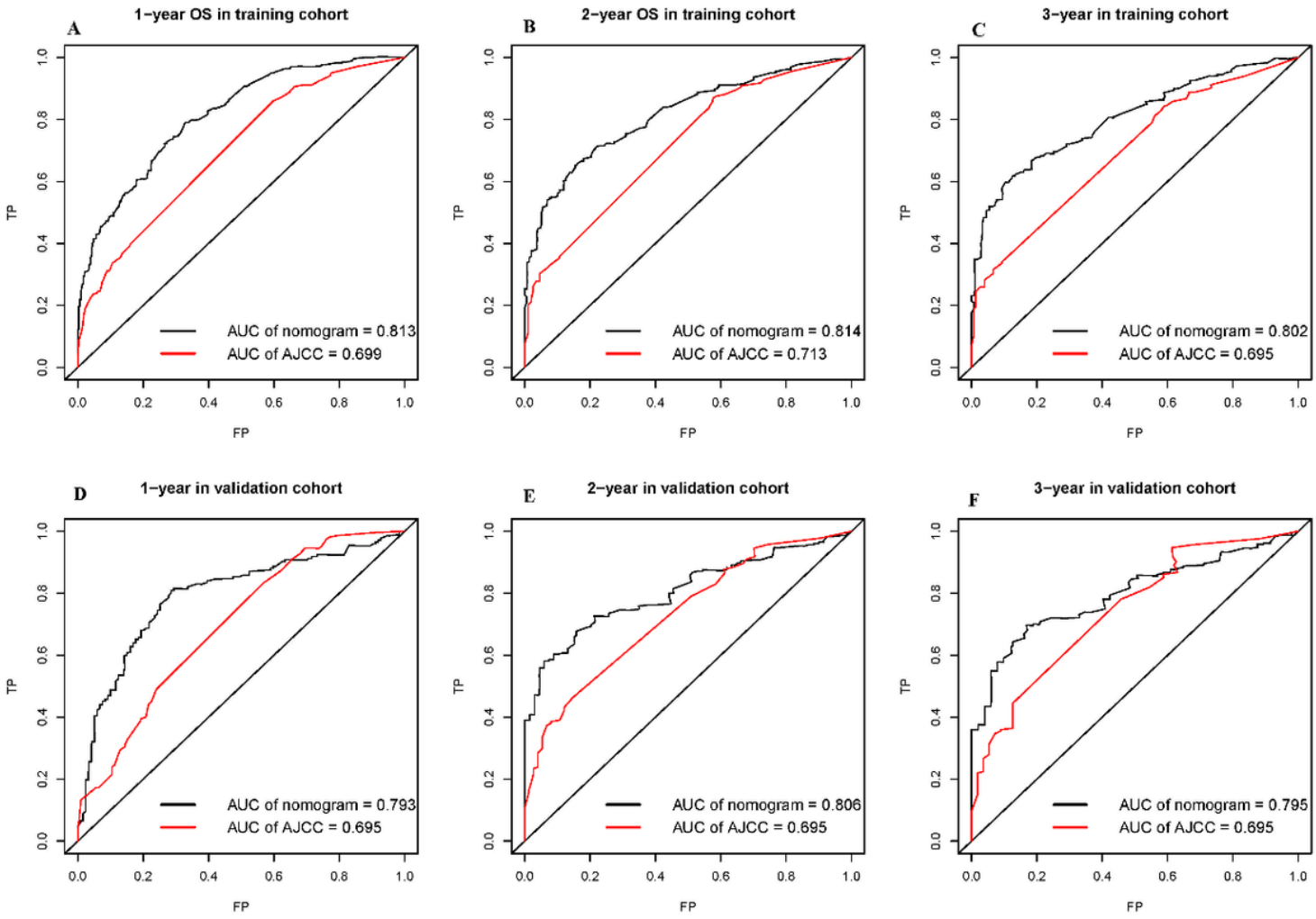

Figure 4

The calibration curves for predicting patients' overall survival in the training cohort (A-C) and validation cohort (D-F) at 1-year, 2-year, and 3-year, respectively.

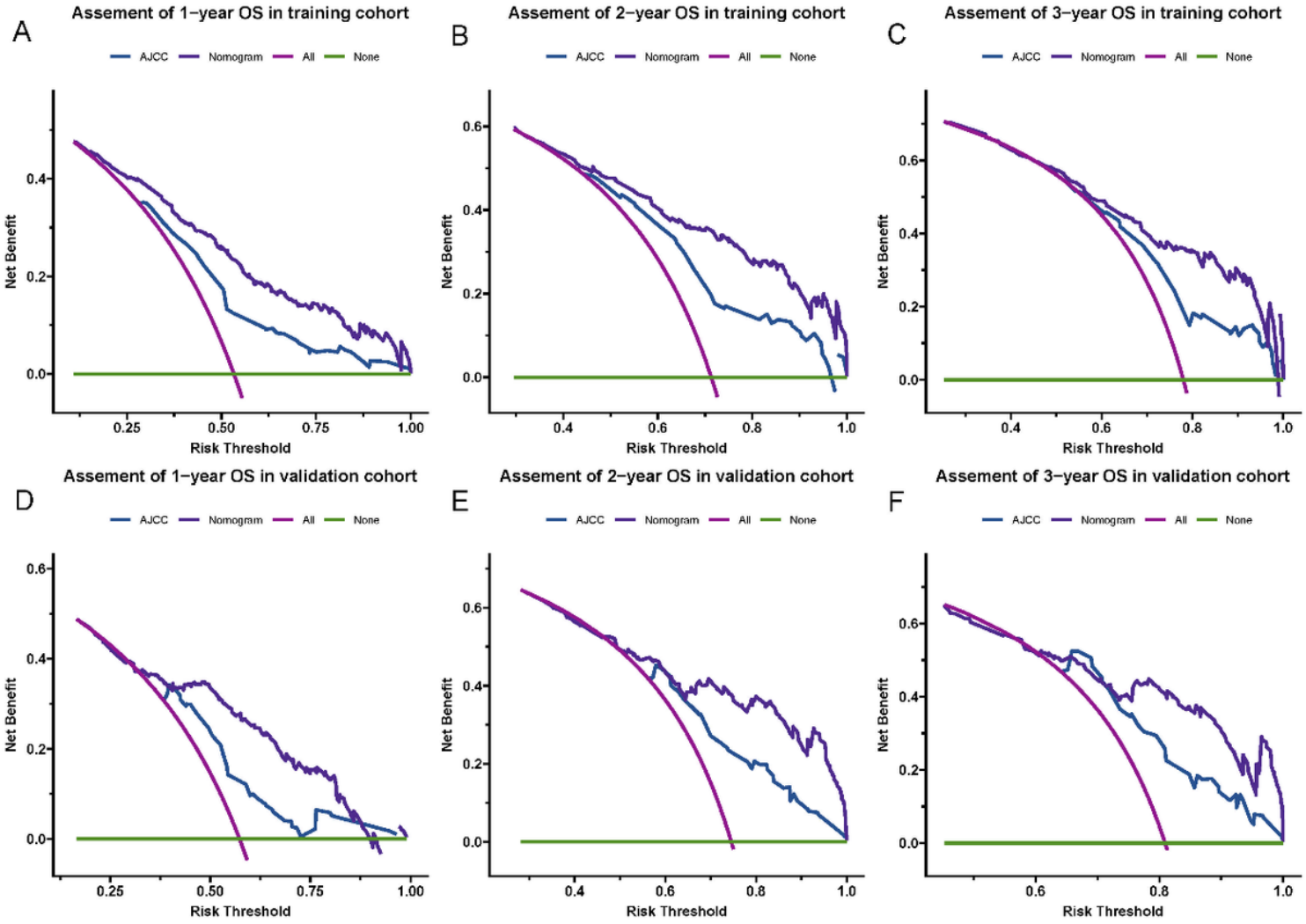

Figure 5

Decision curve analysis for the nomogram and AJCC stage in the prediction of prognosis of male patients at 1-year (A), 2-year (B), and 3-year (A), points in the validation cohorts.

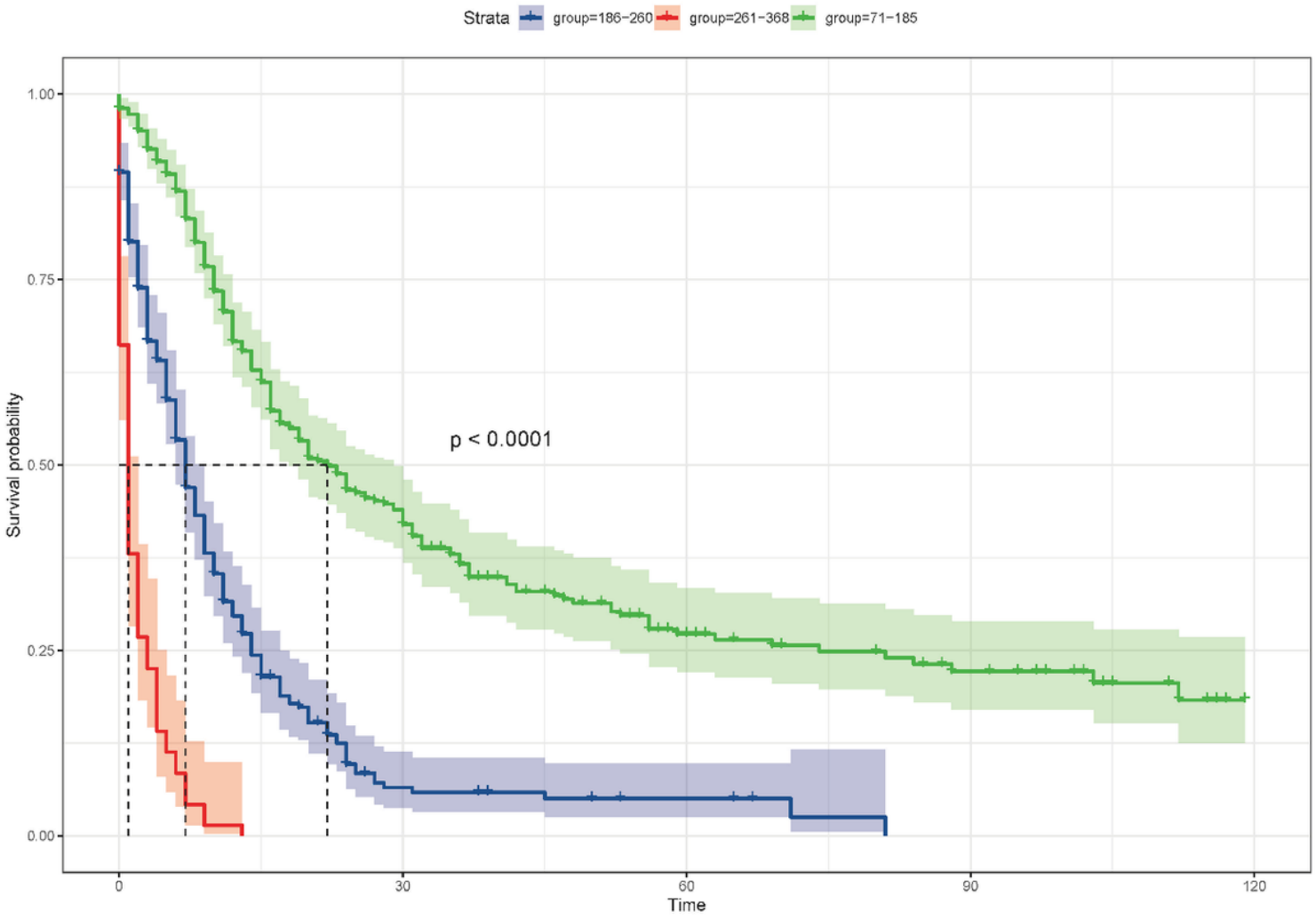

Figure 6

Kaplan–Meier curves of the low-, intermediate- and high-risk groups in training cohorts.