Original Article

Identifying optimal surgical approach among T1N2–3M0 non-small cell lung cancer patients: a population-based analysis

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Background: Whether stage T1N2–3M0 non-small cell lung cancer (NSCLC) patients could benefit from surgery and the optimal surgical procedure have remained controversial and unclear. This study aimed to investigate whether stage T1N2–3M0 NSCLC can benefit from different surgery types and develop a tool for survival prediction.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients diagnosed with stage T1N2–3M0 NSCLC between 2000 and 2015. A 1:1 propensity score-matched (PSM) analysis was used to balance the distribution of clinical characteristics. Survival analyses were performed by using the Kaplan-Meier (KM) curves and Cox proportional hazards regression. All patients were randomly split at a ratio of 7:3 into training and validation cohorts. The nomogram was constructed by integrating all independent predictors for overall survival (OS) and cancer-specific survival (CSS). The model's performance was evaluated by discrimination, calibration ability, and risk stratification ability.

Results: A total of 4,671 patients were enrolled. After 1:1 PSM, the distribution proportions of clinical characteristics in 1,146 patients were balanced (all P>0.05). The non-surgical approach was associated with worse survival compared with sublobectomy and lobectomy in the unmatched and matched cohorts. The multivariate Cox analysis showed that sublobectomy and lobectomy were both related to better OS and CSS rates compared with no surgery (P<0.001). Moreover, the results of subgroup analyses based on age, N stage, and radiotherapy or chemotherapy strategy were consistent. A total of 801 patients were included in the training cohort and 345 cases constituted the validation cohort. The nomogram constructed for the 1-, 3-, and 5-year OS and CSS prediction showed good discrimination, performance, and calibration both in the training and validation sets. Significant distinctions in survival curves between different risk groups stratified by prognostic scores were also observed (all P<0.001).

Conclusions: Stage T1N2–3M0 NSCLC patients could benefit from sublobectomy or lobectomy, and lobectomy provides better survival benefits. We developed and validated nomograms, which could offer clinicians instructions for strategy making.

Keywords: Lobectomy; sublobectomy; non-small cell lung cancer (NSCLC); prognosis; nomogram

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Introduction

Lung cancer continues to be the foremost contributor to cancer-related fatalities worldwide (1). Non-small cell lung cancer (NSCLC) is the predominant subtype, constituting roughly 80–85% of lung cancer cases (2). As health awareness among individuals improves and low-dose spiral computed tomography (CT) screening gains popularity among long-term smokers, the likelihood of detecting smaller lung cancers has significantly increased (3). However, despite the improved detection of small tumor sizes through CT screening, some patients present with lymph node metastasis at the time of diagnosis. For individuals with early-stage NSCLC (stages I–II), the standard approach involves surgery followed by adjuvant chemotherapy for those with large primary tumors or positive lymph nodes. The 5-year survival rate for this subgroup of patients ranges from approximately 50% to 75% (4).

Stage III NSCLC accounts for approximately 30% of patients diagnosed with NSCLC, which represents an intermediate phase between clearly resectable early-stage disease and metastatic involvement (5). The precise criteria for surgical treatment in this stage remain a subject of considerable debate, despite the completion of randomized controlled trials (RCTs) (6). Concurrent chemotherapy and radiotherapy are considered the standard of care for patients with satisfactory performance status and are viewed as potentially curative (7). Surgical resection can offer optimal local control and confer survival advantages beyond chemotherapy and radiation alone for suitable surgical candidates (8). A phase III RCT published by Albain *et al*. compared concurrent chemotherapy and radiotherapy followed by resection with standard concurrent chemotherapy and definitive radiotherapy without resection, revealing that progression-free survival was better in the surgery group than in the non-surgery group (9). Bott *et al.* also suggested that surgical resection as a part of multimodality therapy may be associated with improved OS in highly selected patients with stage IIIB NSCLC (10). Subsequently, a report published by Caglar *et al.* also suggested that stage III NSCLC patients who were candidates for resection appeared to achieve better outcomes following the induction of concurrent chemoradiation (11). But there is currently a paucity of conclusive studies regarding whether surgery benefits T1N2–3M0 patients and what the optimal surgical approach might be. In our study, we aimed to determine the survival advantages of surgery in T1N2–3M0 NSCLC patients, utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/), and to visually represent the benefits of surgical intervention. We present this article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-213/rc).

Highlight box

Key findings

- Determining the survival advantages of surgery in T1N2–3M0 non-small cell lung cancer (NSCLC) patients and visually representing the benefits of surgical intervention.

What is known and what is new?

- Concurrent chemotherapy and radiotherapy are considered as the standard and viewed as potentially curative. The surgical benefit in T1N2–3M0 NSCLC patients remained a subject of considerable debate.
- We identified the survival benefits of different surgical approaches in T1N2–3M0 NSCLC patients, and provided a valuable tool for obtaining personalized survival estimates and more personalized treatment strategies.

What is the implication, and what should change now?

- Our predictive model enhances the understanding of the differential benefits associated with various surgical approaches and provides clinicians instructions for the personalized treatment of T1N2–3M0 NSCLC patients.

Methods

Patient selection

The SEER database is a national population-based reporting system that collects tumor-related data, including the incidence, treatment, mortality, and other demographics, covering around 28% of the US population and presenting information on the incidence of cancer in 18 regions across the US, which can help decrease incidence of tumors (12). The SEER database contains no identifiers and is publicly available for studies of cancer-related survival analysis. The patients diagnosed with NSCLC from 2000 to 2015 were identified from the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study population included patients with the following International Classification of Disease for Oncology Third Edition (ICD-O-3), morphology codes: 8010, 8012–8014, 8020–8022, 8050–8052, 8070–8078,

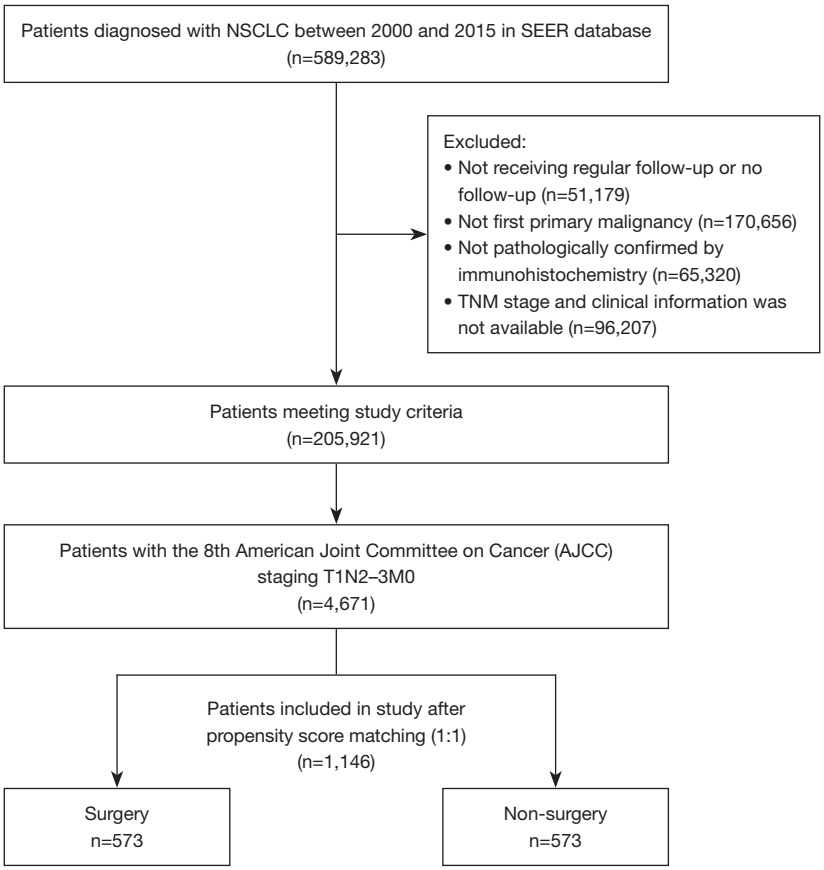


Figure 1 Flowchart for data filtration of T1N2–3M0 NSCLC patients. NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; TNM, tumor-node-metastasis.

8140–8147, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, 8572. Patients diagnosed as stage T1N2–3M0 and histologically confirmed as having NSCLC were enrolled. The exclusion criteria were as follows: (I) patients without complete information concerning follow-up; (II) patients with a history of at least one previous malignancy; (III) not diagnosed by immunohistochemical pathology; and (IV) patients lacking information concerning primary lesion size (T), regional lymph node (N), or distant metastasis (M) stage and other clinically relevant information (*Figure 1*).

Variables

To make data analysis convenient, we transformed continuous variables into categorical variables. The extracted clinical information included sex, age, race, site, tumor laterality, grade, T stage, N stage, lymph node dissection (LND), histology, radiotherapy, chemotherapy, survival months, causes of death, and survival status. As for surgical approach, the resection of less than one lobe was defined as sublobectomy because some surgical procedures were unclear in the SEER database, or the number of cases was too small to analyze separately. The tumor-node-metastasis (TNM) stage was reclassified according to the American Joint Committee on Cancer (AJCC) 8th edition, based on tumor size, tumor collaborative stage (CS) extension, and the 6/7th edition N/M stages (13). Due to the absence of treatment sequence, we cannot determine radiotherapy and chemotherapy as neoadjuvant or adjuvant therapy. The time of the last follow-up was November 2020. Overall survival (OS) was defined as the interval between cancer diagnosis and death resulting from any

cause or the last follow-up for patients still alive. Cancer-specific survival (CSS) was defined as the length of time between cancer diagnosis and death from NSCLC.

Development and validation of a nomogram

According to our exclusion criteria, the eligible patients after propensity score matching (PSM) were randomly divided into training and validation cohorts at a ratio of 7:3. The nomogram was developed using the training cohort of 801 patients and the validation cohort of 345 patients was used to validate the model. We performed a univariate Cox proportional hazard regression analysis to identify independent prognostic factors of OS and CSS. Significant factors in univariate analysis were included in the multivariate Cox proportional hazard regression analysis in order to acquire the hazard ratio (HR) and corresponding 95% confidential interval (CI) for each independent prognostic factor. The nomograms for predicting OS and CSS were developed using the risk factors calculated from the final multivariate Cox regression model.

The concordance index (C-index) was used to evaluate the performance for predicting the survival of this nomogram model, which indicates a measure of concordance. And it is similar to the area under the receiver operating characteristic (ROC) curve. The theoretical value of the C-index ranges from 0 to 1.0, and larger values of the C-index indicates better predictive performance (14). The calibration curves were plotted to assess the consistency between predicted survival probability and actual survival proportion in the training and validation cohort. A model that is perfectly calibrated would display a 45-degree curve. Discrimination and calibration were estimated by bootstrapping 1,000 times. Decision curve analysis (DCA) was also performed to assess the improved benefits and performance of the nomograms (15).

In the training cohort, we grouped patients into three risk subsets based on prognostic scores to evaluate the model's discriminative ability. The cut-off values were determined using the X-tile software 3.6.1 (Copyright: Camp/Rimm; Yale University, New Haven, CT, USA). The cut-off values were also subsequently applied to the validation cohort. The difference in survival was assessed by calculating the respective log-rank P values. These data analyses were also performed using R Studio version 4.1.2 (RStudio, Boston, MA, USA). The R packages 'survival', 'rms', 'riskRegression', 'survminer', and 'ggDCA' were used for nomogram construction and evaluation. Furthermore, the R packages 'DynNom', 'DNbuilder', and 'rsconnect' were applied to develop a user-friendly web-based interface for our nomogram.

Statistical analysis

The patients were divided according to whether they received surgery versus non-surgery treatment of the primary tumor. The baseline characteristics of patients in the surgery group and the non-surgery group were described using frequencies and percentages. We performed PSM to balance potential bias and possible confounding interference between the two groups, with a caliper width of 0.008 (16). Patients in the two groups (surgery and non-surgery) were 1:1 matched using the nearest propensity score on the logit scale. Variables used for matching were sex, age, race, site, laterality, grade, T stage, N stage, LND, histology, radiotherapy, and chemotherapy. The difference of demographic data among the two groups were assessed for significance using the Student's *t*-test or χ^2 test and the Fisher's exact test before and after PSM. The distinctions of OS and CSS were estimated by applying the Kaplan-Meier (K-M) method with the log-rank test. The Cox proportional hazards regression analyses with both univariate and multivariate Cox regression analyses were used to determine independent prognostic factors. HRs were calculated with 95% CIs. All data analyses were performed using R Studio version 4.1.2. A two-sided P value <0.05 was deemed significant.

Results

The characteristics of patients before and after PSM

A total of 589,283 patients with NSCLC were identified in the SEER database spanning from 2000 to 2015, of whom 4,671 met the criteria for T1N2–3M0 NSCLC (*Figure 1*). Among these T1N2–3M0 NSCLC patients, the majority were male, aged 65 years or younger, of white race, and had tumors located on the right side and in the upper lobe. These tumors were predominantly of the adenocarcinoma subtype and were poorly differentiated. Among the eligible patients, only 2,034 (43.55%) underwent surgical treatment. Notably, there were significant differences in various factors including age, sex, race, tumor site, laterality, grade,

N stage, LND, histology, and radiotherapy between the two treatment groups before performing PSM. Surgical intervention was more common among patients aged 65 years or younger and those with lower N stage. A higher proportion of female patients received surgical treatment. Additionally, compared to the non-surgery group, the surgery group had a higher prevalence of white race, adenocarcinoma histology, left-sided tumors, lower lobe location, and moderately differentiated tumors. Notably, the majority (88.89%) of patients who underwent surgery also had LND. Within the surgery group, 949 (46.66%) patients received radiotherapy. There was no statistically significant difference between the two treatment groups regarding the use of chemotherapy. These data reveal that the baseline characteristics of the two groups (surgery and non-surgery) were initially imbalanced (*Table 1*).

After implementing 1:1 PSM, a total of 1,146 T1N2–3M0 NSCLC patients, treated with or without surgery, were included in the analysis. Following PSM, baseline characteristics, including sex, age, race, tumor site, laterality, grade, T stage, N stage, LND, histology, radiotherapy, and chemotherapy, were all well-balanced (P>0.05). Furthermore, we observed that the majority of T1N2–3M0 NSCLC patients were male, aged >65 years, of white race, with right-sided upper lobe tumors, and predominantly had adenocarcinoma histology and poorly differentiated tumors. Most of the tumors measured 2–3 cm. More than half of the patients had N2-positive status and received both chemotherapy and radiotherapy. The detailed information is presented in *Table 2*.

Surgical treatment as an independent prognostic factor for survival in T1N2–3M0 NSCLC patients

In the univariate analysis, several factors including sex, age, race, grade, histology, surgery, radiotherapy, and chemotherapy exhibited significant associations with OS, as presented in *Table 3*. These same factors, with the exception of histology and radiotherapy, were also found to be significantly associated with CSS (*Table 3*). Following multivariate analysis, variables such as sex, age, race, grade, surgery, radiotherapy, and chemotherapy were confirmed to be independently associated with OS (*Table 4*). Specifically, individuals aged over 65 years, male, of white race, with poorly differentiated or undifferentiated tumors, and who did not undergo surgery or receive chemotherapy were identified as having a higher hazard of death due to lung cancer, as indicated by the results of multivariate analysis (*Table 4*). The site and laterality of the tumor, extent of lymph node removal, histological subtype, T stage, N stage, and radiotherapy were not found to have a significant impact on CSS. Regarding surgical procedures, it was observed that lobectomy was associated with the lowest risk of death, whereas other surgical approaches also demonstrated improvements in both OS and CSS among T1N2–3M0 NSCLC patients.

Table 1 The clinicopathologic characteristics of T1N2–3M0 NSCLC patients before PSM

Characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	P value
All	4,671 (100.00)	2,637 (56.45)	2,034 (43.55)	
Sex				<0.001
Female	2,295 (49.13)	1,214 (46.04)	1,081 (53.15)	
Male	2,376 (50.87)	1,423 (53.96)	953 (46.85)	
Age (years)				<0.001
≤65	2,056 (44.02)	1,019 (38.64)	1,037 (50.98)	
>65	2,615 (55.98)	1,618 (61.36)	997 (49.02)	
Race				0.02
White	3,793 (81.20)	2,134 (80.93)	1,659 (81.56)	
Black	537 (11.50)	328 (12.44)	209 (10.28)	
Other	341 (7.30)	175 (6.64)	166 (8.16)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	P value
Site				<0.001
Upper lobe	2,998 (64.18)	1,704 (64.62)	1,294 (63.62)	
Middle lobe	249 (5.33)	141 (5.35)	108 (5.31)	
Lower lobe	1,274 (27.27)	687 (26.05)	587 (28.86)	
Main bronchus	102 (2.18)	88 (3.34)	14 (0.69)	
Overlapping lesion	48 (1.03)	17 (0.64)	31 (1.52)	
Laterality				<0.001
Right	2,790 (59.73)	1,634 (61.96)	1,156 (56.83)	
Left	1,881 (40.27)	1,003 (38.04)	878 (43.17)	
Grade				<0.001
Well	305 (6.53)	175 (6.64)	130 (6.39)	
Moderate	1,656 (35.45)	786 (29.81)	870 (42.77)	
Poor	2,538 (54.34)	1,563 (59.27)	975 (47.94)	
Undifferentiated	172 (3.68)	113 (4.29)	59 (2.90)	
T stage				0.68
T1a	88 (1.88)	46 (1.74)	42 (2.06)	
T1b	1,898 (40.63)	1,079 (40.92)	819 (40.27)	
T1c	2,685 (57.48)	1,512 (57.34)	1,173 (57.67)	
N stage				<0.001
N2	3,979 (85.19)	2,010 (76.22)	1,969 (96.80)	
N3	692 (14.81)	627 (23.78)	65 (3.20)	
LND				<0.001
Yes	2,268 (48.55)	460 (17.44)	1,808 (88.89)	
No	2,403 (51.45)	2,177 (82.56)	226 (11.11)	
Histology				<0.001
ADC	2,676 (57.29)	1,254 (47.55)	1,422 (69.91)	
SCC	1,211 (25.93)	869 (32.95)	342 (16.81)	
Other	784 (16.78)	514 (19.49)	270 (13.27)	
Radiotherapy				<0.001
Yes	2,633 (56.37)	1,684 (63.86)	949 (46.66)	
No/unknown	2,038 (43.63)	953 (36.14)	1,085 (53.34)	
Chemotherapy				0.68
Yes	3,040 (65.08)	1,709 (64.81)	1,331 (65.44)	
No/unknown	1,631 (34.92)	928 (35.19)	703 (34.56)	

NSCLC, non-small cell lung cancer; PSM, propensity score matching; LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

Table 2 The clinicopathologic characteristics of T1N2–3M0 NSCLC patients after PSM

Characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	P value
All	1,146 (100.00)	573 (50.00)	573 (50.00)	
Sex				0.29
Female	553 (48.25)	286 (49.91)	267 (46.60)	
Male	593 (51.75)	287 (50.09)	306 (53.40)	
Age (years)				0.63
≤65	503 (43.89)	256 (44.68)	247 (43.11)	
>65	643 (56.11)	317 (55.32)	326 (56.89)	
Race				0.15
White	934 (81.50)	479 (83.60)	455 (79.41)	
Black	137 (11.95)	63 (10.99)	74 (12.91)	
Other	75 (6.54)	31 (5.41)	44 (7.68)	
Site				0.22
Upper lobe	725 (63.26)	376 (65.62)	349 (60.91)	
Middle lobe	69 (6.02)	27 (4.71)	42 (7.33)	
Lower lobe	316 (27.57)	150 (26.18)	166 (28.97)	
Main bronchus	24 (2.09)	14 (2.44)	10 (1.75)	
Overlapping lesion	12 (1.05)	6 (1.05)	6 (1.05)	
Laterality				0.51
Right	698 (60.91)	355 (61.95)	343 (59.86)	
Left	448 (39.09)	218 (38.05)	230 (40.14)	
Grade				0.17
Well	95 (8.29)	41 (7.16)	54 (9.42)	
Moderate	372 (32.46)	201 (35.08)	171 (29.84)	
Poor	626 (54.62)	303 (52.88)	323 (56.37)	
Undifferentiated	53 (4.62)	28 (4.89)	25 (4.36)	
T stage				0.14
T1a	24 (2.09)	8 (1.40)	16 (2.79)	
T1b	459 (40.05)	222 (38.74)	237 (41.36)	
T1c	663 (57.85)	343 (59.86)	320 (55.85)	
N stage				0.70
N2	1027 (89.62)	511 (89.18)	516 (90.05)	
N3	119 (10.38)	62 (10.82)	57 (9.95)	
LND				0.95
Yes	696 (60.73)	349 (60.91)	347 (60.56)	
No	450 (39.27)	224 (39.09)	226 (39.44)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	P value
Histology				0.84
ADC	668 (58.29)	339 (59.16)	329 (57.42)	
SCC	288 (25.13)	141 (24.61)	147 (25.65)	
Other	190 (16.58)	93 (16.23)	97 (16.93)	
Radiotherapy				0.15
Yes	649 (56.63)	337 (58.81)	312 (54.45)	
No/unknown	497 (43.37)	236 (41.19)	261 (45.55)	
Chemotherapy				0.19
Yes	774 (67.54)	398 (69.46)	376 (65.62)	
No/unknown	372 (32.46)	175 (30.54)	197 (34.38)	

NSCLC, non-small cell lung cancer; PSM, propensity score matching; LND, lymph nodes dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

Table 3 Univariable Cox regression analysis for OS and CSS of T1N2–3M0 NSCLC patients after PSM

Variables	Univariate (OS)		Univariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.74 (0.65–0.83)	<0.001	0.74 (0.65–0.85)	<0.001
Age (years)				
≤65	1		1	
>65	1.34 (1.18–1.52)	<0.001	1.25 (1.09–1.44)	0.001
Race				
White	1		1	
Blank	0.81 (0.66–0.98)	0.03	0.84 (0.68–1.04)	0.11
Other	0.62 (0.48–0.81)	0.001	0.63 (0.47–0.84)	0.002
Site				
Lower lobe	1		1	
Upper lobe	0.93 (0.80–1.07)	0.30	0.92 (0.79–1.08)	0.32
Middle lobe	0.95 (0.72–1.25)	0.70	1.03 (0.77–1.38)	0.85
Main bronchus	1.22 (0.79–1.88)	0.37	1.27 (0.79–2.03)	0.32
Overlapping lesion	1.50 (0.82–2.73)	0.19	1.44 (0.74–2.80)	0.28
Laterality				
Left	1		1	
Right	0.97 (0.86–1.10)	0.64	0.97 (0.84–1.11)	0.64

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Univariate (OS)		Univariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Grade				
Well	1		1	
Moderate	1.79 (1.38–2.33)	<0.001	1.64 (1.24–2.18)	<0.001
Poor	1.89 (1.47–2.43)	<0.001	1.72 (1.31–2.25)	<0.001
Undifferentiated	1.96 (1.35–2.84)	<0.001	1.88 (1.26–2.81)	0.002
T stage				
T1a	1		1	
T1b	1.19 (0.75–1.89)	0.45	1.32 (0.77–2.25)	0.31
T1c	1.38 (0.87–2.17)	0.17	1.55 (0.91–2.63)	0.11
N stage				
N2	1		1	
N3	1.10 (0.90–1.35)	0.34	1.17 (0.94–1.45)	0.15
Surgery				
Non-surgery	1		1	
Sublobectomy	0.71 (0.59–0.85)	<0.001	0.65 (0.52–0.80)	<0.001
Lobectomy	0.53 (0.46–0.60)	<0.001	0.48 (0.41–0.56)	<0.001
LND				
No	1		1	
Yes	0.90 (0.79–1.02)	0.09	0.94 (0.82–1.08)	0.39
Histology				
ADC	1		1	
SCC	1.25 (1.08–1.45)	0.003	1.15 (0.98–1.36)	0.09
Other	1.00 (0.84–1.20)	0.96	1.03 (0.85–1.24)	0.77
Radiotherapy				
Yes	1		1	
No	1.18 (1.04–1.34)	0.008	1.14 (1.00–1.31)	0.056
Chemotherapy				
Yes	1		1	
No	1.31 (1.15–1.50)	<0.001	1.20 (1.04–1.39)	0.01

OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

Table 4 Multivariable Cox regression analysis for OS and CSS of T1N2–3M0 NSCLC patients after PSM

Variables	Multivariate (OS)		Multivariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.74 (0.65–0.84)	<0.001	0.74 (0.64–0.85)	<0.001
Age (years)				
≤65	1		1	
>65	1.31 (1.15–1.49)	<0.001	1.25 (1.09–1.44)	<0.001
Race				
White	1		1	
Blank	0.88 (0.72–1.07)	0.20	0.91 (0.73–1.13)	0.40
Other	0.64 (0.49–0.84)	0.001	0.65 (0.48– 0.87)	<0.001
Grade				
Well	1		1	
Moderate	1.77 (1.35–2.30)	<0.001	1.58 (1.19–2.09)	<0.001
Poor	2.01 (1.55–2.60)	<0.001	1.73 (1.31–2.26)	<0.001
Undifferentiated	2.29 (1.53–3.41)	<0.001	1.84 (1.23–2.76)	<0.001
Surgery				
Non-surgery	1		1	
Sublobectomy	0.65 (0.54–0.78)	<0.001	0.61 (0.49–0.75)	<0.001
Lobectomy	0.50 (0.44–0.58)	<0.001	0.47 (0.41–0.55)	<0.001
Histology				
ADC	1			
SCC	1.05 (0.90–1.22)	0.52		
Other	0.84 (0.69–1.02)	0.08		
Radiotherapy				
Yes	1			
No	1.20 (1.05–1.37)	0.008		
Chemotherapy				
Yes	1		1	
No	1.32 (1.15–1.52)	<0.001	1.28 (1.10–1.48)	<0.001

OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

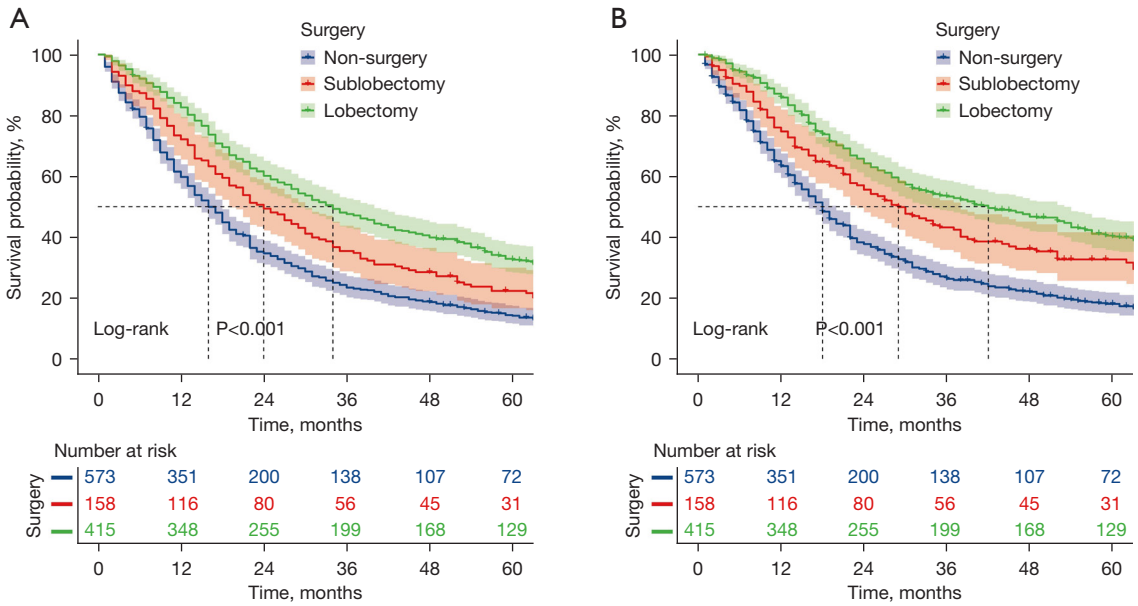


Figure 2 Survival analyses of OS and CSS for T1N2–3M0 NSCLC patients stratified by surgery strategy after PSM. (A) KM curves of OS. (B) KM curves of CSS. OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; PSM, propensity score matching; KM, Kaplan-Meier.

Impact of tumor resection on survival outcomes in T1N2–3M0 NSCLC patients

In the KM analyses and log-rank tests conducted on a matched patient population, as illustrated in Figure S1 and *Figure 2*, patients who underwent either lobectomy or sublobectomy exhibited significantly prolonged OS and CSS compared to those who did not receive surgery, both before and after PSM. After PSM, the median CSS time for patients who underwent lobectomy was 42 months (95% CI: 32.32–51.68), whereas for patients who did not receive surgery, it was only 18 months (95% CI: 16.14–19.86) (P<0.001). The median OS time for patients who underwent lobectomy was 34 months (95% CI: 28.91–39.09), whereas for those who did not undergo surgery, it was only 16 months (95% CI: 14.28–17.72) (P<0.001). In summary, the median OS times for patients with no surgery, sublobectomy, or lobectomy were 16, 24, and 34 months, respectively, and the median CSS times were 18, 29, and 42 months, respectively.

To further determine the protective effect of surgical procedures on OS and CSS, we conducted subgroup analysis among different age groups, N stages, and treatment categories after PSM. Across various age groups, the surgery group consistently demonstrated better prognoses than the non-surgery group for both OS and CSS (*Figure 3A-3D*), with the exception of patients aged >65 years. However, it is noteworthy that within all age groups, the trend favored lobectomy over sublobectomy in terms of survival benefits. When considering different N-stage categories, the surgery group exhibited improved prognoses compared to the non-surgery group for both OS and CSS in all cases. In the N2 subgroup analysis, we found that the lobectomy group presented improved OS compared with the sublobectomy group (*Figure 4A*), and the lobectomy group also exhibited better OS compared with the sublobectomy group in the N3 subgroup (*Figure 4B*). The CSS subgroup analysis showed that the sublobectomy group presented a similar survival compared with the lobectomy group in N2-positive patients (*Figure 4C*), whereas the lobectomy group exhibited improved prognosis compared with the sublobectomy group in N3-positive patients (*Figure 4D*). In terms of treatment regimens, the surgery group presented better OS and CSS than the non-surgery group except for the patients who received radiotherapy alone. The difference in OS and CSS outcomes was not significant between the sublobectomy and non-surgery groups in patients who received chemotherapy alone or chemotherapy plus radiotherapy,

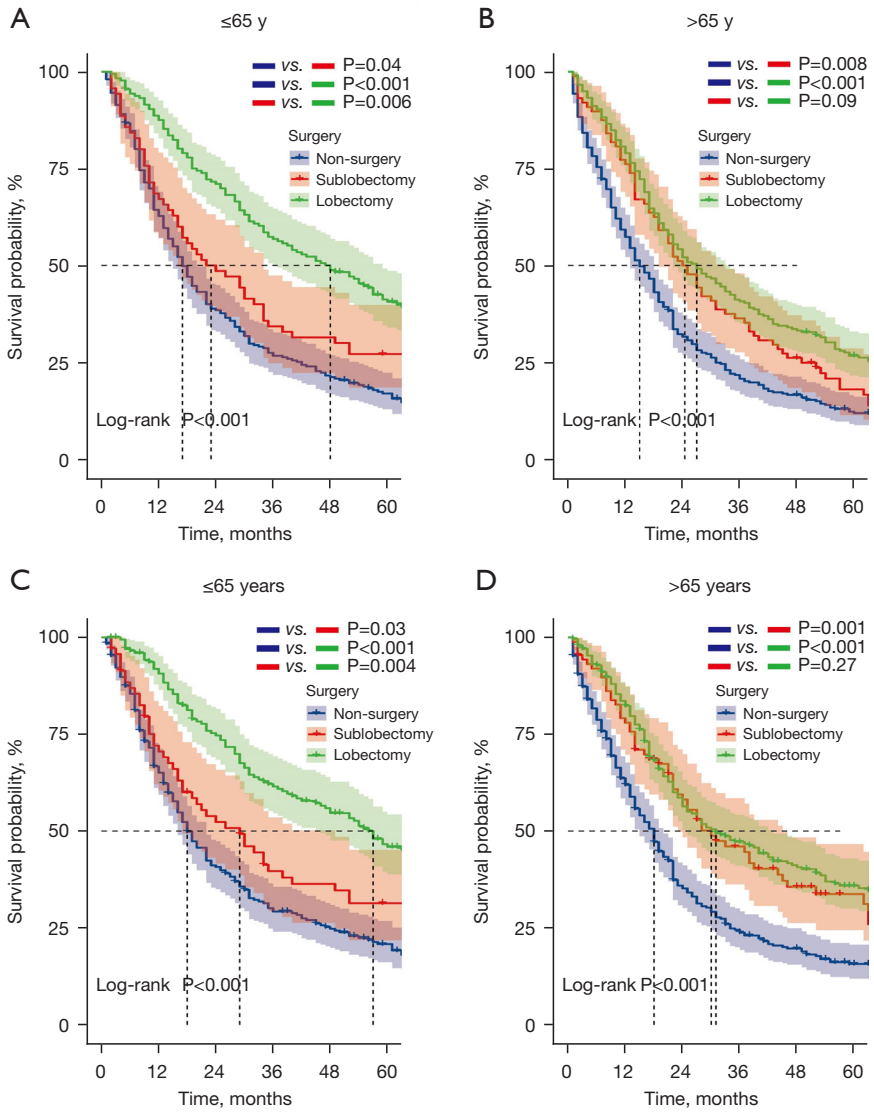


Figure 3 KM analyses of OS (A,B) and CSS (C,D) for T1N2–3M0 NSCLC patients aged ≤65 years old (A,C) and >65 years old (B,D) stratified by surgery strategy. KM, Kaplan-Meier; OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer.

although the trend favored sublobectomy for both OS and CSS. In the KM analyses of OS, lobectomy did not provide improved survival compared with sublobectomy in patients with chemotherapy (*Figure 5A*). For patients in the radiotherapy group, the surgery group could not achieve better survival than the non-surgery group (*Figure 5B*). However, the lobectomy provided improved survival compared to sublobectomy in patients with chemotherapy plus radiotherapy (*Figure 5C*). For the patients without radiotherapy and chemotherapy, the lobectomy exhibited similar survival compared with the sublobectomy (*Figure 5D*). In the KM analyses of CSS, lobectomy achieved better CSS than sublobectomy in patients who underwent single chemotherapy (*Figure 5E*), whereas surgery did not improve the prognosis compared with the non-surgery group in patients with single radiotherapy (*Figure 5F*). The outcomes of sublobectomy and non-surgery were comparable whereas lobectomy showed superior survival outcome compared with sublobectomy for patients underwent chemotherapy plus radiotherapy (*Figure 5G*). For the patients without radiotherapy and chemotherapy, the lobectomy and

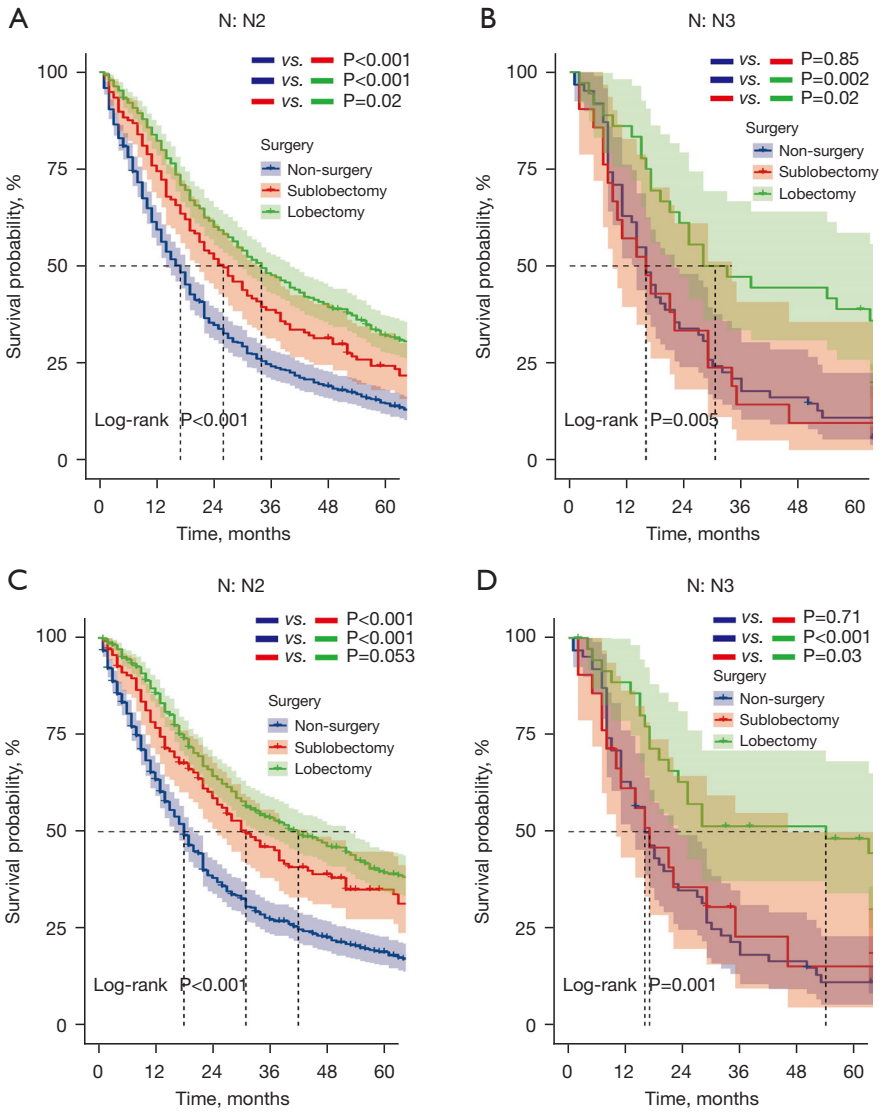
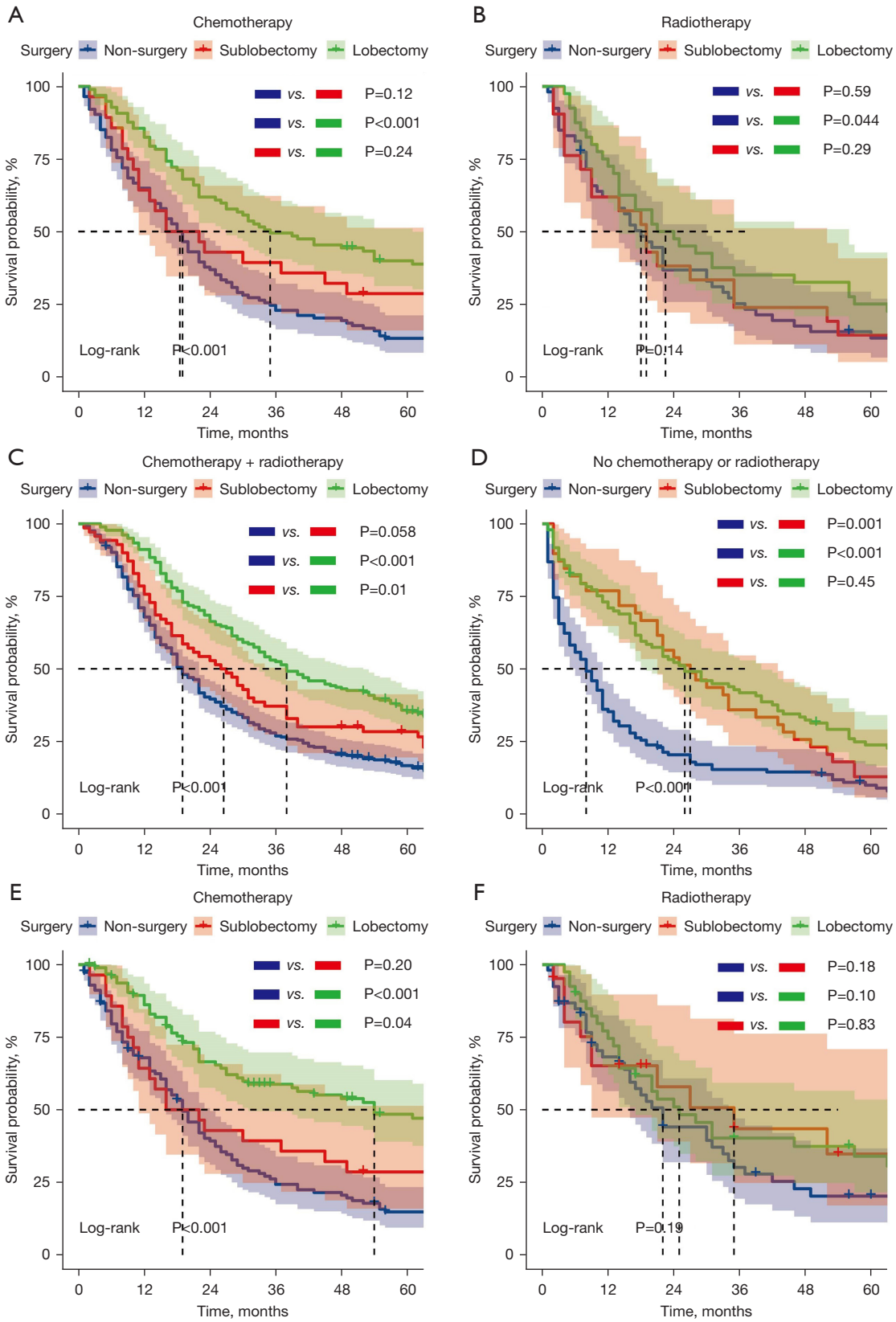


Figure 4 KM analyses of OS (A,B) and CSS (C,D) for T1N2–3M0 NSCLC patients with N2 stage (A,C) and N3 stage (B,D) stratified by surgery strategy. KM, Kaplan-Meier; OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer.

sublobectomy group achieved better CSS than non-surgery group and the similar results of lobectomy and sublobectomy are displayed in *Figure 5H*. Overall, these findings provide valuable insights into the benefits of surgery for T1N2–3M0 NSCLC patients, taking into account various clinical factors and treatment modalities.

Nomogram to visualize the benefits of different surgical approaches in T1N2-3M0 NSCLC patients

A total of 1,146 T1N2–3M0 NSCLC patients were randomly assigned to the training set (n=801) and the validation set (n=345) in a 7:3 ratio. In comparing the training and validation cohorts, the demographic variables were insignificant (*Table 5*) (all P>0.05). Within the training cohort, there were 707 recorded events, specifically patient deaths, and out of these, 583 patients succumbed to cancer. The mean follow-up duration for these patients was 38.18 months, with a range spanning from 1 to 217 months. In univariate analysis, sex, age, race, grade, surgery, histology, and chemotherapy were significantly associated with OS. These factors were also significantly associated with CSS



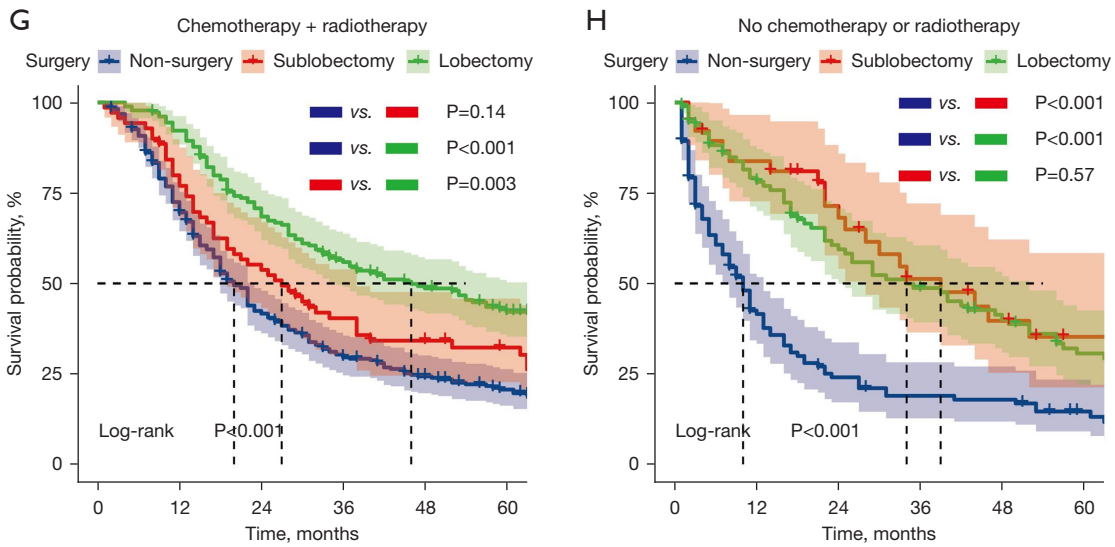


Figure 5 KM analyses of OS (A-D) and CSS (E-H) for T1N2–3M0 NSCLC patients with chemotherapy (A,E), radiotherapy (B,F), chemotherapy plus radiotherapy (C,G), and no chemotherapy or radiotherapy (D,H) stratified by surgical strategy. KM, Kaplan-Meier; OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer.

Table 5 Demographic and clinicopathologic characteristics of the training and validation cohort

Characteristics	Training cohort, n (%)	Validation cohort, n (%)	P value
Number of cases	801	345	
Sex			0.52
Female	381 (47.57)	172 (49.86)	
Male	420 (52.43)	173 (50.14)	
Age (years)			0.36
≤65	344 (42.95)	159 (46.09)	
>65	457 (57.05)	186 (53.91)	
Race			0.91
White	652 (81.40)	282 (81.74)	
Black	95 (11.86)	42 (12.17)	
Other	54 (6.74)	21 (6.09)	
Site			0.45
Upper lobe	516 (64.42)	209 (60.58)	
Middle lobe	49 (6.12)	20 (5.80)	
Lower lobe	214 (26.72)	102 (29.57)	
Main bronchus	16 (2.00)	8 (2.32)	
Overlapping lesion	6 (0.75)	6 (1.74)	

Table 5 (*continued*)

Table 5 (*continued*)

Characteristics	Training cohort, n (%)	Validation cohort, n (%)	P value
Laterality			0.08
Right	474 (59.18)	224 (64.93)	
Left	327 (40.82)	121 (35.07)	
Grade			0.39
Well	59 (7.37)	36 (10.43)	
Moderate	262 (32.71)	110 (31.88)	
Poor	442 (55.18)	184 (53.33)	
Undifferentiated	38 (4.74)	15 (4.35)	
T stage			0.65
T1a	18 (2.25)	6 (1.74)	
T1b	326 (40.70)	133 (38.55)	
T1c	457 (57.05)	206 (59.71)	
N stage			0.95
N2	717 (89.51)	310 (89.86)	
N3	84 (10.49)	35 (10.14)	
LND			0.51
Yes	481 (60.05)	215 (62.32)	
No	320 (39.95)	130 (37.68)	
Histology			0.33
ADC	456 (56.93)	212 (61.45)	
SCC	210 (26.22)	78 (22.61)	
Other	135 (16.85)	55 (15.94)	
Radiotherapy			0.69
Yes	450 (56.18)	199 (57.68)	
No/unknown	351 (43.82)	146 (42.32)	
Chemotherapy			0.24
Yes	532 (66.42)	242 (70.14)	
No/unknown	269 (33.58)	103 (29.86)	

LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

except for the factor of histology and chemotherapy (*Table 6*). Given the recognized impact of chemotherapy on patient prognosis in previous literature, we included this factor in the subsequent multivariate analysis. After the multivariate analysis, the most significant variables for the development of the nomogram model for OS were identified as sex, age, grade, surgery, and chemotherapy, as depicted in *Figure 6A* and *Table* 7. For the nomogram model for CSS, the significant variables included sex, grade, surgery, and chemotherapy, as shown in *Figure 6B* and *Table* 7.

Each of these variables was assigned a point score ranging from 0 to 100. In both the OS and CSS nomograms, the grade of tumor differentiation had the most substantial

Table 6 Univariable Cox regression analysis for OS and CSS of T1N2–3M0 NSCLC patients in the training cohort

Variables	Univariate (OS)		Univariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.69 (0.60–0.80)	<0.001	0.70 (0.59–0.82)	<0.001
Age (years)				
≤65	1		1	
>65	1.23 (1.06–1.43)	0.007	1.36 (1.19–1.56)	<0.001
Race				
White	1		1	
Blank	0.89 (0.7–1.11)	0.30	0.89 (0.69–1.15)	0.38
Other	0.62 (0.46–0.85)	0.003	0.64 (0.45–0.9)	0.01
Site				
Lower lobe	1		1	
Upper lobe	0.93 (0.78–1.1)	0.73	0.95 (0.78–1.14)	0.57
Middle lobe	0.96 (0.69–1.34)	0.72	1.03 (0.72–1.47)	0.87
Main bronchus	1.46 (0.86–2.47)	0.99	1.63 (0.95–2.83)	0.08
Overlapping lesion	2.43 (1.08–5.49)	0.46	2.40 (0.99–5.86)	0.054
Laterality				
Left	1		1	
Right	1.02 (0.87–1.18)	0.84	1.04 (0.88–1.22)	0.67
Grade				
Well	1		1	
Moderate	1.85 (1.33–2.57)	<0.001	1.65 (1.16–2.35)	0.005
Poor	2.1 (1.53–2.89)	<0.001	1.83 (1.30–2.58)	0.001
Undifferentiated	2.72 (1.74–4.27)	<0.001	2.53 (1.56–4.1)	<0.001
T stage				
T1a	1		1	
T1b	1.10 (0.65–1.84)	0.73	1.21 (0.66–2.22)	0.53
T1c	1.28 (0.77–2.15)	0.35	1.46 (0.8–2.65)	0.22
N stage				
N2	1		1	
N3	0.96 (0.75–1.23)	0.75	1.02 (0.78–1.33)	0.89

Table 6 (*continued*)

Table 6 (*continued*)

Variables	Univariate (OS)		Univariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgery				
Non-surgery	1		1	
Sublobectomy	0.68 (0.54–0.85)	0.001	0.61 (0.48–0.79)	<0.001
Lobectomy	0.57 (0.48–0.67)	<0.001	0.51 (0.42–0.61)	<0.001
LND				
No	1		1	
Yes	0.90 (0.77–1.04)	0.15	0.98 (0.83–1.16)	0.80
Histology				
ADC	1		1	
SCC	1.32 (1.11–1.57)	0.002	1.18 (0.97–1.43)	0.10
Other	1.10 (0.89–1.35)	0.38	1.14 (0.92–1.43)	0.24
Radiotherapy				
Yes	1		1	
No	1.16 (1–1.34)	0.056	1.11 (0.94–1.31)	0.21
Chemotherapy				
Yes	1		1	
No	1.25 (1.07–1.45)	0.006	1.16 (0.98–1.38)	0.09

OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

contribution to the prognosis, being assigned a maximum score of 100, followed by the type of surgical procedure performed. Notably, the impact of the surgical procedure was more pronounced in the nomogram model for CSS compared to OS, with a score of 91. It is worth highlighting that lobectomy had a substantial influence on the prediction of survival for both CSS and OS, followed by sublobectomy. Each factor can obtain a corresponding point by drawing a line straight upward to the "point axis". The individual risk scores were calculated by summing up the score of each variable. The probabilities of survival at 1-, 3-, and 5-year were easily determined by locating their corresponding point on the survival scale.

Model performance and validation of the nomogram

In the training cohort, the C-indexes for the established nomogram were 0.699 (95% CI: 0.646–0.751), 0.674 (95% CI: 0.630–0.717), and 0.697 (95% CI: 0.646–0.748) for predicting 1-, 3-, and 5-year OS, respectively, as depicted in *Figure 7A*. In the validation cohort, these C-indexes were 0.703 (95% CI: 0.642–0.765), 0.683 (95% CI: 0.636–0.729), and 0.694 (95% CI: 0.641–0.747), respectively, as shown in *Figure 7B*. For predicting 1-, 3-, and 5-year CSS, the C-indexes in the training cohort were 0.709 (95% CI: 0.630–0.787), 0.764 (95% CI: 0.700–0.827), and 0.761 (95% CI: 0.692–0.830), respectively (*Figure 7C*). In the validation cohort, these C-indexes were 0.704 (95% CI: 0.611–0.797), 0.728 (95% CI: 0.654–0.802), and 0.708 (95% CI: 0.630–0.786), as displayed in *Figure 7D*. The calibration plots at 1-, 3-, and 5-year OS showed excellent consistency in the training cohort (*Figure 8A*) and acceptable consistency in the validation cohort (*Figure 8B*) between the predicted survival probability and actual observation. Similar results could be seen in the calibration plots at 1-, 3-, and 5-year CSS in the training cohort (*Figure 8C*) and the validation cohort (*Figure 8D*). Additionally, DCA revealed that our nomogram model offered practical and wide ranges of

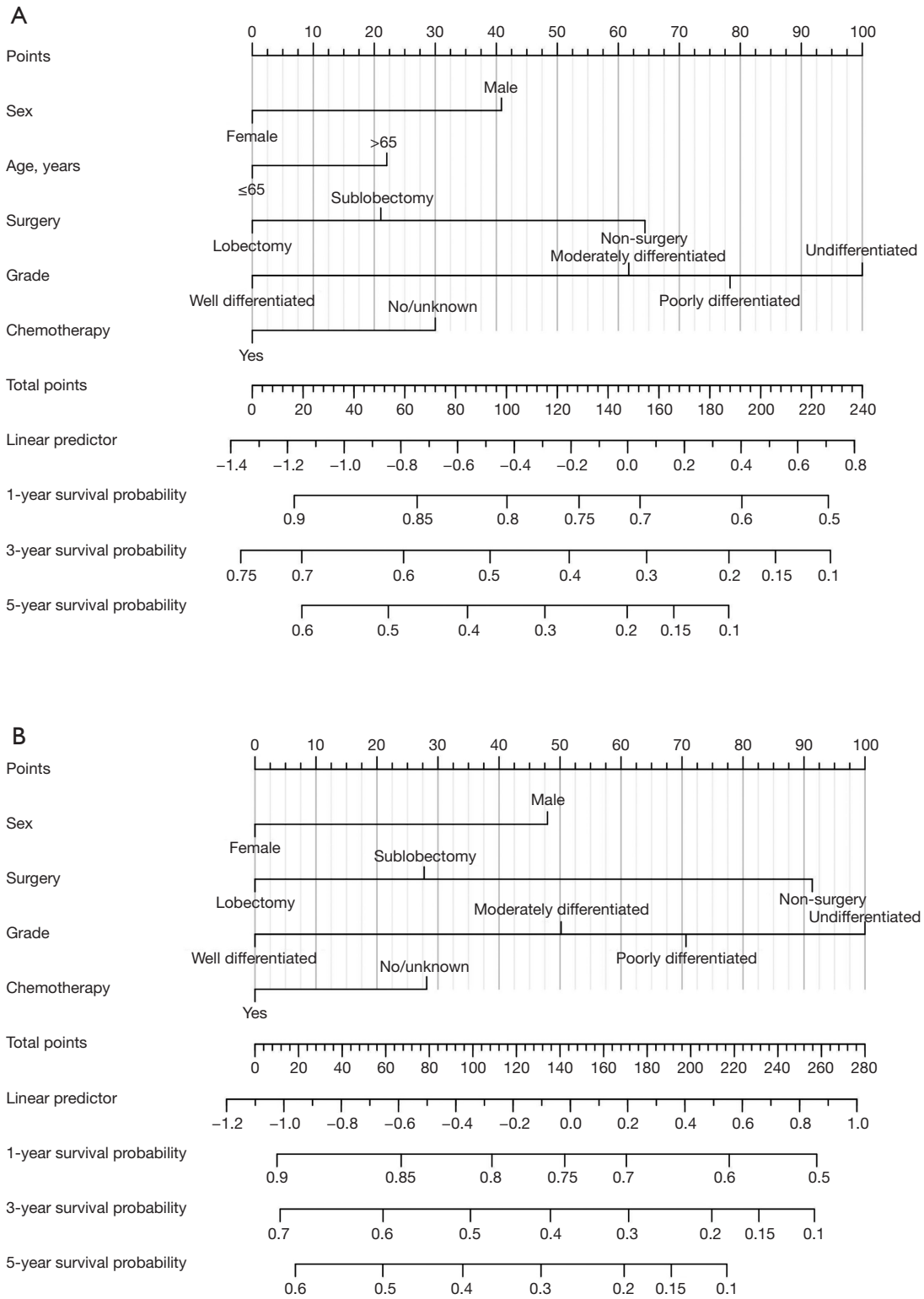


Figure 6 Nomograms to predict 1-, 3-, and 5-year (A) OS and (B) CSS probability for T1N2–3M0 NSCLC patients. OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer.

Table 7 Multivariable Cox regression analysis for OS and CSS of T1N2–3M0 NSCLC patients in the training cohort

Variables	Multivariate (OS)		Multivariate (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.70 (0.60–0.81)	<0.001	0.68 (0.58–1.80)	<0.001
Age (years)				
≤65	1		1	
>65	1.22 (1.05–1.43)	0.01	1.14 (0.97–1.35)	0.12
Race				
White	1		1	
Blank	1.00 (0.79–1.26)	0.99	0.98 (0.76–1.27)	0.88
Other	0.62 (0.45–0.86)	0.003	0.62 (0.44–0.87)	0.007
Grade				
Well	1		1	
Moderate	1.70 (1.21–2.38)	0.002	1.49 (1.04–2.12)	0.03
Poor	2.02 (1.46–2.81)	<0.001	1.72 (1.22–2.43)	0.002
Undifferentiated	2.71 (1.67–4.40)	<0.001	2.20 (1.35–3.59)	0.002
Surgery				
Non-surgery	1		1	
Sublobectomy	0.66 (0.52–0.83)	<0.001	0.60 (0.47–0.78)	<0.001
Lobectomy	0.56 (0.47–0.66)	<0.001	0.50 (0.42–0.60)	<0.001
Histology				
ADC	1			
SCC	1.09 (0.91–1.30)	0.37		
Other	0.89 (0.71–1.12)	0.33		
Radiotherapy				
Yes				
No				
Chemotherapy				
Yes	1		1	
No	1.30 (1.10–1.52)	0.002	1.21 (1.01–1.44)	0.04

OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; LND, lymph node dissection; ADC, adenosquamous carcinoma; SCC, squamous cell carcinoma.

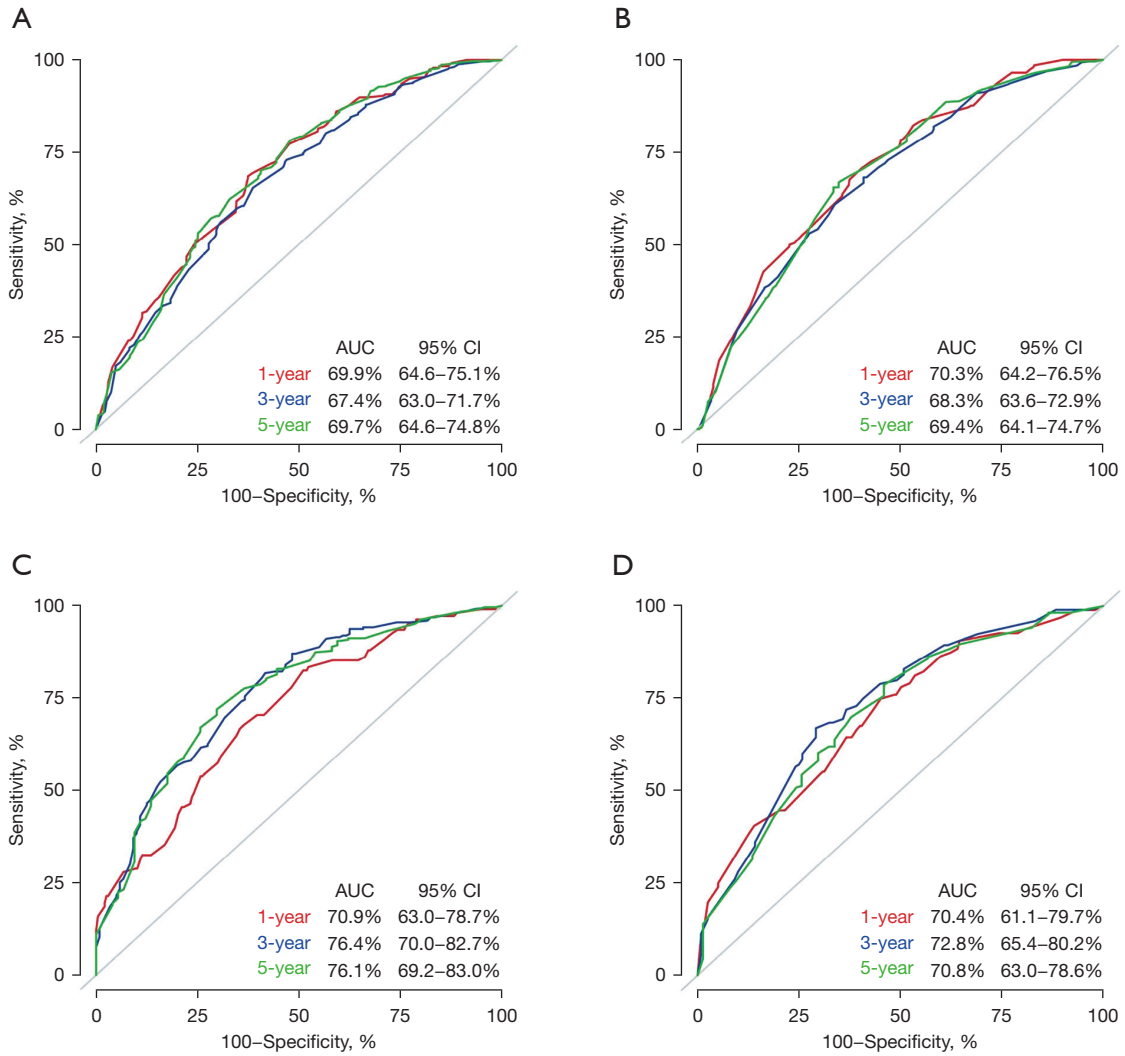


Figure 7 Model performance of the proposed nomogram. Time-dependent ROC curves of the prognostic models for predicting 1- (red), 3- (blue), and 5-year (green) OS (A,B) and CSS (C,D). The AUCs of the prognostic models at each time point of interest were presented in the training (A,C) and validation cohorts (B,D). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; OS, overall survival; CSS, cancer-specific survival.

threshold probabilities regardless of OS (*Figure 9A-9C*) and CSS (*Figure 9D-9F*). This further confirmed the clinical applicability and performance of our nomogram in predicting patient prognosis.

Risk-stratifying ability of the nomogram

Based on the total predictive risk scores, we subcategorized the training cohort into three risk groups, including low-, middle-, and high-risk groups, with the optimal cut-off values developed from X-tile software. Detailed subgroups of CSS were 0–91.5, 98.0–189.5, and 190.5–267.5, and OS were 0–124.0, 125.0–197.0, and 205.0–235.0 (Figure S2). The same stratification method was subsequently applied to the validation cohort. The survival curves for OS showed significant differences between any two adjacent groups in the training cohort and the validation cohort (P<0.0001; *Figure 10A,10B*). Significant distinctions in the survival curves for CSS were also observed between different risk groups in the training cohort and the validation cohort

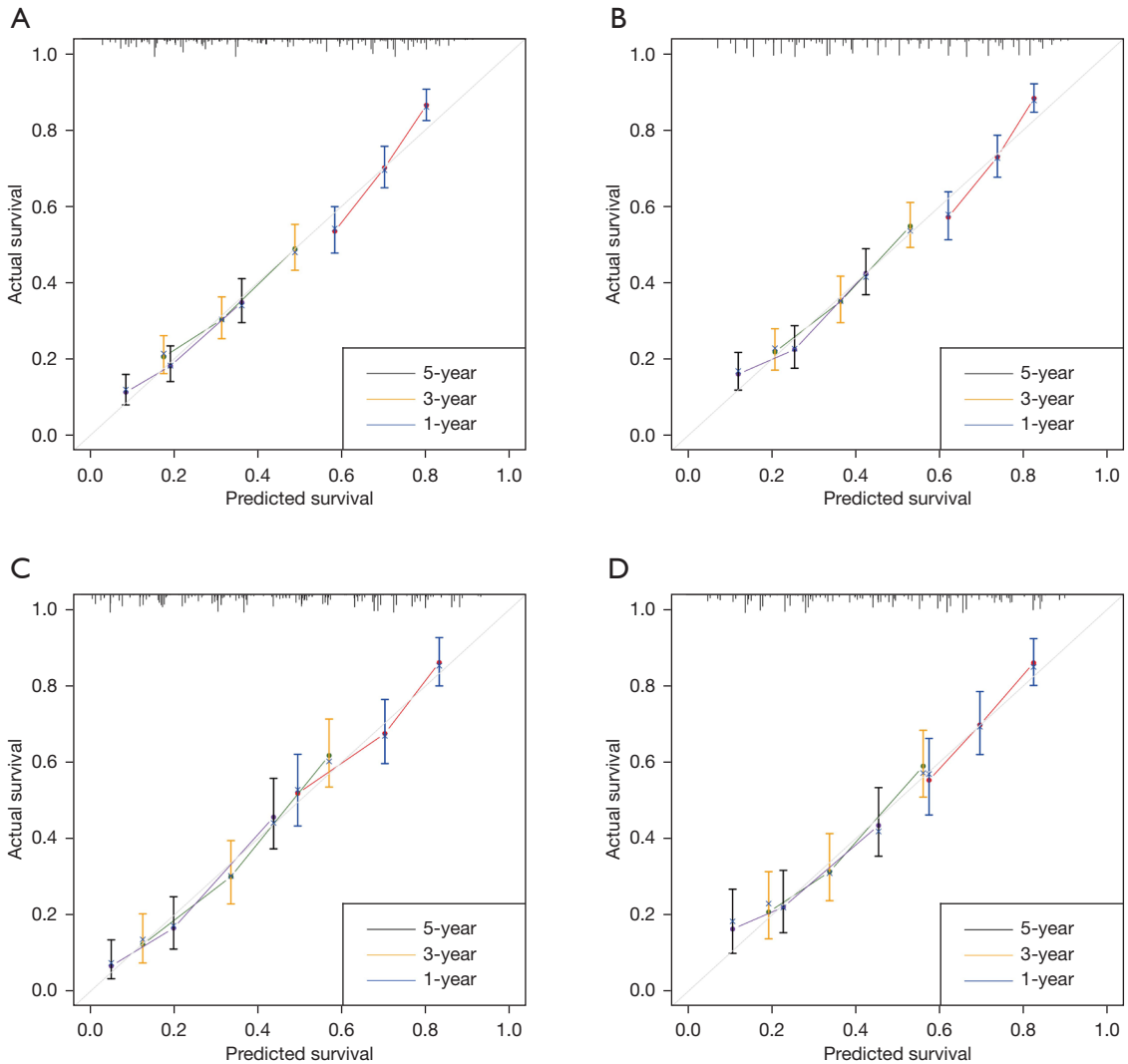


Figure 8 Nomogram calibration curves for nomogram-predicted survival (X-axis) and actual observed survival (Y-axis). Calibration curves for OS (A,B) and CSS (C,D) in the training (A,C) and validation cohort (B,D); curves for 1-, 3-, and 5-year OS and CSS were present as blue, yellow, and black lines, respectively. OS, overall survival; CSS, cancer-specific survival.

(P<0.0001; *Figure 10C,10D*).

Webserver development for the nomogram

For the sake of user convenience, we have developed a user-friendly website that facilitates the easy calculation of individualized survival probabilities for T1N2–3M0 NSCLC patients. To obtain personalized survival estimates, users simply need to input specific clinical variables pertaining to the patient in question, along with a desired prediction time frame in months. Additionally, the website generates corresponding survival plots for the provided case. The public online version of our nomogram is accessible via the following links: https://shanghaisuzhousclcnomogrampredictability.shinyapps.io/Nomogram/ and https://shanghaisuzhousclcnomogrampredictability.shinyapps.io/Nomogramcss/. We have made these websites freely available for clinicians and users, eliminating the need for any password input. It is important to note that this tool may offer clinicians instructions for survival counseling and treatment strategy making conveniently, but we should

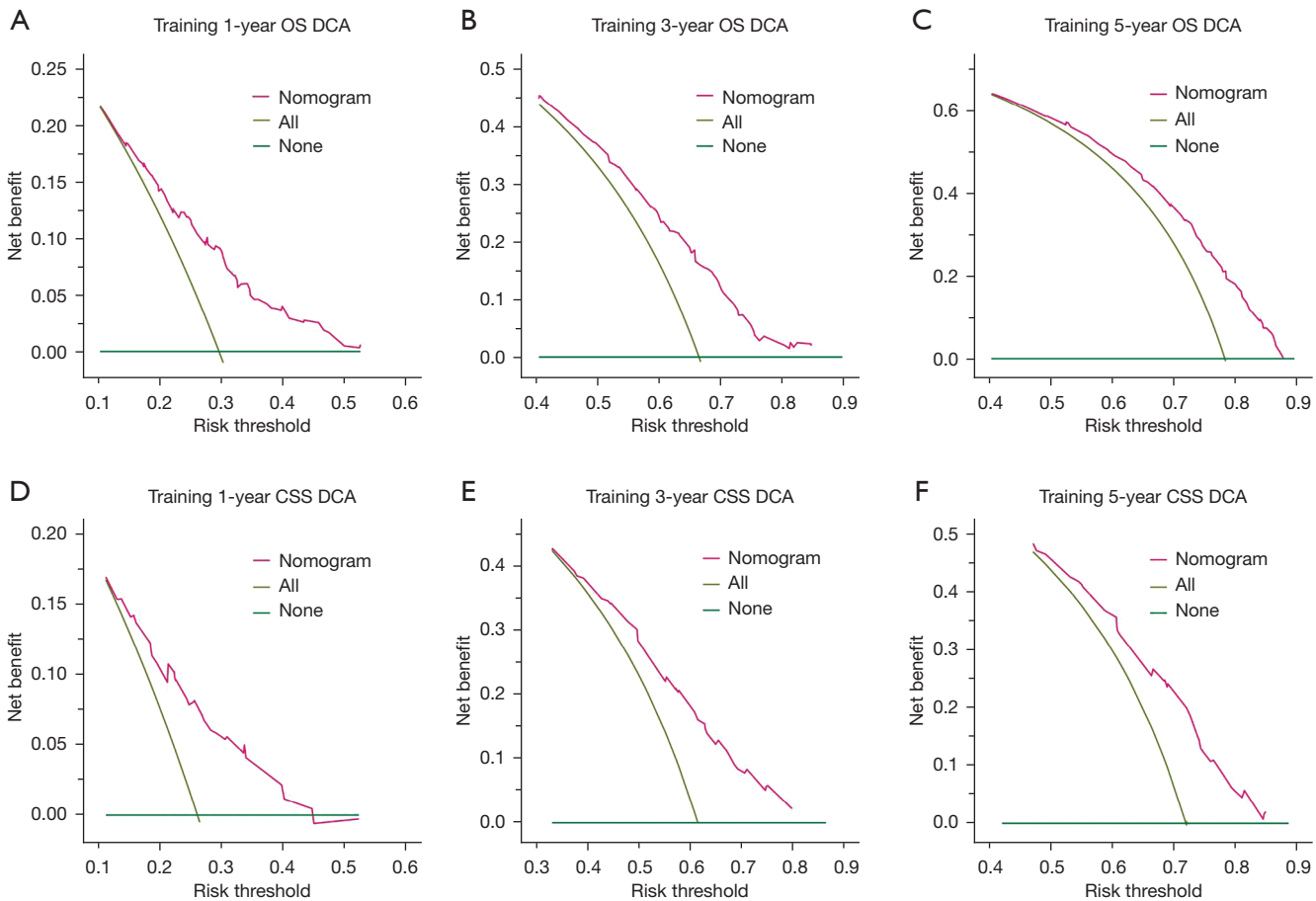


Figure 9 DCA curves of the proposed nomogram for 1-, 3-, and 5-year OS (A-C) and CSS (D-F). The green horizontal solid line along the X-axis assumes that overall death occurred in no patients, whereas the light green solid line assumes that all patients will have overall death at a specific threshold probability. OS, overall survival; DCA, decision curve analysis; CSS, cancer-specific survival.

apply it to clinical practice cautiously before its predictive capacity has been validated in prospective, large-sample RCTs.

Discussion

Stage III NSCLC patients constitute a highly diverse group with varying survival outcomes, primarily due to the significant heterogeneity observed in factors such as tumor size, the extent of lymph node involvement, and the level of lymph node engagement. The choice between surgical intervention with adjuvant chemoradiotherapy and concurrent chemoradiotherapy alone has typically been made on a case-by-case basis. Consequently, determining the optimal treatment approach for T1N2–3M0 NSCLC patients has been a challenging task. Moreover, the debate regarding the potential benefits of lobectomy for stage III NSCLC patients has persisted without strong supporting evidence. Furthermore, there has been a lack of attention given to sublobectomy as a treatment option for this specific patient population. Some previous RCTs have indicated that surgery yields equivalent survival outcomes when compared to non-surgical approaches for stage III NSCLC patients who have undergone chemotherapy or chemoradiotherapy (9,17). However, a retrospective study conducted by Caglar *et al.*, have suggested that stage III NSCLC patients who are eligible for resection may experience improved outcomes following induction concurrent chemoradiotherapy (11). Other retrospective studies have also reported a positive association between surgery and enhanced survival (18-20). To comprehensively investigate the role of surgery in T1N2–3M0 NSCLC patients, we conducted this study

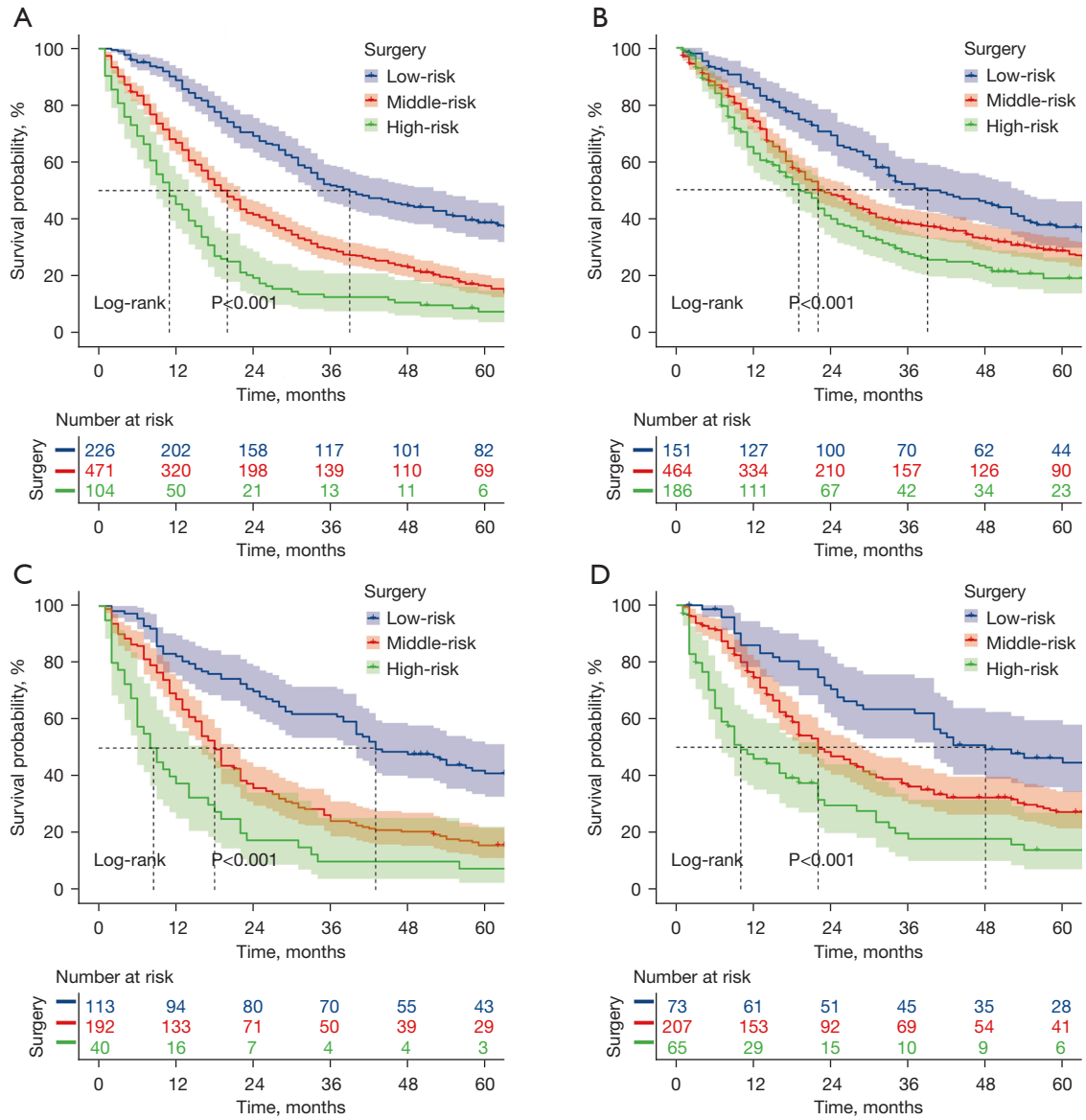


Figure 10 KM survival curves for OS (A,B) and CSS (C,D) in the training (A,C) and validation (B,D) cohorts to test the risk stratification system based on the training cohort. KM, Kaplan-Meier; OS, overall survival; CSS, cancer-specific survival.

using a large cohort of patients, utilizing data from the SEER database. Additionally, we developed a predictive nomogram model to visualize the potential survival benefits of surgery. This model can aid in providing survival counseling for patients and clinicians, informing the design of clinical trials, guiding postoperative strategies, and contributing to the advancement of precision medicine for T1N2–3M0 NSCLC patients.

There is existing literature supporting the use of radical anatomical segmentectomy, particularly in elderly patients with limited cardiopulmonary function (21,22). In specific patient subsets, segmentectomy has been shown to be oncologically equivalent to lobectomy while offering the advantage of better preservation of pulmonary function (23). Our study revealed that both sublobectomy and lobectomy were associated with improved rates of OS and CSS. Subgroup analyses based on factors such as age, N stage, and the administration of radiotherapy or chemotherapy consistently supported these findings. Notably, a multicenter retrospective study led by Behera *et al.*, based on the

National Cancer Database, found that chemoradiotherapy followed by lobectomy or pneumonectomy was linked to superior survival outcomes compared to chemoradiotherapy alone, which aligns with the results of our subgroup analysis (4). However, there is currently no definitive study elucidating the survival advantages of different surgical approaches in T1N2–3M0 NSCLC patients. Our study was the first to demonstrate that sublobectomy confers a survival benefit when compared to the non-surgery group. Therefore, sublobectomy may still be a viable consideration for stage T1N2–3M0 NSCLC patients, particularly those of advanced age or with compromised cardiopulmonary function, even though lobectomy offers a more favorable survival prognosis. Nonetheless, further validation through multicenter RCTs is necessary to confirm the benefits of both lobectomy and sublobectomy for these patients.

The guidelines provided by the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) recommend definitive concurrent chemoradiation and immunotherapy as the initial therapy for N3-stage NSCLC (24,25). A recent study also showed that immunotherapy-based treatments in the neoadjuvant period could downstage initially unresectable NSCLC, converting into resectable disease and improve the prognosis in patients who received surgery (26). For patients confirmed to have N2 disease, upfront surgical resection has traditionally been considered infeasible because the tumor is unresectable and is not recommended (4). However, there is limited literature available on the outcomes of surgery for these patients. In cases where patients exhibit microscopic or minimal nodal involvement, induction therapy followed by surgical resection is recommended (4). Notably, the study by Caglar *et al.* indicated that the rate of local recurrence for IIIA–IIIB patients who received chemoradiotherapy or chemoradiotherapy followed by surgery was 50% and 7%, respectively (11). Similarly, Raman *et al.* found that surgery is associated with comparable or slightly worse short-term survival but improved long-term survival compared to chemoradiation in selected patients with N3 NSCLC (27). A retrospective study conducted by Fu *et al.* reported that patients with stage IIIA–N2 NSCLC treated with upfront surgery followed by adjuvant therapy showed promising long-term outcomes (28). Despite these recommendations and findings, the rate of surgery for T1N2–3M0 NSCLC patients remains low. In our study, only 29.8% of T1N2–3M0 NSCLC patients underwent surgical treatment, indicating that a minority of these specific patients could potentially benefit from surgery. The management of T1N2–3M0 NSCLC patients requires a multidisciplinary approach involving medical oncologists, thoracic surgeons, and radiation oncologists to assess the potential benefits of surgery and the resectability of the tumor (29). Given the heterogeneity within the T1N2–3M0 NSCLC stage, characterized by variations in the extent and location of nodal involvement, the decision to pursue surgery should be made carefully and on a case-by-case basis.

In our study, another intriguing finding was that sublobectomy did not significantly improve OS or CSS compared to the non-surgery group in patients with N3-positive disease. A prospective study of stage III NSCLC by Grunenwald *et al.* indicated that patients with N2 and N3 disease exhibited similar rates of mediastinal node sterilization, which suggests that patients with N3 disease may have tumor behavior more aligned with N2 rather than T4 disease and could potentially benefit from multimodal therapy, including surgery (30). Additionally, mounting evidence suggests that downstaging of mediastinal nodes is associated with improved prognosis (31,32). Therefore, lobectomy may be the preferred surgical approach for patients with N3-positive disease, even when the tumor size is less than 3 cm. However, for N2-positive patients with limited cardiopulmonary function, sublobectomy could still be a viable option.

Lung cancer is a highly heterogeneous disease, and its treatment should be tailored to the individual patient. Our study represents the first attempt to establish a prediction model for the long-term survival of T1N2–3M0 NSCLC patients and visualize the benefits of different treatment strategies specifically for this subset of patients. In our study, the calibration curve showed optimal agreement between predicted survival and actual observation, demonstrating good repeatability and reliability of this established model. Furthermore, these nomograms fit well in the validation cohort, which represent the universalized application of the models. Our nomogram models represented practical and wide ranges of threshold probabilities regardless of OS and CSS, although the C-index of our models failed to reach a high magnitude. It is noteworthy that when the validation dataset was stratified into different risk groups using the optimal cut-off values from the training cohort, significant differences in the survival curves were observed, which indicates the satisfactory discriminative ability of these models. According to the scoring system developed from our model, these models could offer a valuable tool for survival prediction, identifying high-risk patients with poor prognosis, improving precision medicine, and enhancing

the prognosis of this unique patient group. Meanwhile, our model for different treatment modalities may not be suitable for direct use, as the decision on treatment involves multiple factors, not just these factors. And because of the limited sample size for constructing the model in our study, the relevant conclusions may not be applicable to all patients. But the relevant conclusions can provide some reference for treatment strategy making.

So far, there have been several published nomograms concerning survival prediction for N2/N3 positive NSCLC. Mao *et al.* developed and validated a nomogram that could provide an individual prediction of OS for stage IIIA–N2 NSCLC patients after surgery (33). Han *et al.* reported a clinicopathologic prediction model for the survival of patients with the N3 stage (34). These previous models were not exclusively designed for T1N2–3M0 NSCLC patients and did not include specific surgical approaches. Therefore, they may not be entirely suitable for predicting survival in this particular patient population. In our nomogram, we included a substantial number of T1N2–3M0 NSCLC patients from the SEER database containing approximately 28% of the United States (US) population (12), which could maintain the generalizability of our model. Furthermore, our model incorporates a comprehensive panel of clinicopathologic variables, including surgical approaches, to ensure accuracy and reliability. Notably, our model is the first to conduct the prediction of CSS, providing valuable insights into the most beneficial treatment modalities and a more precise estimation of survival probabilities for these patients. Independent validation of our model yielded an ideal C-index, demonstrating its generalizability and predictive accuracy.

Some common independent prognostic factors for locally advanced NSCLC, such as age, sex, and histology, have been included in several published models (35-37). Our model also identified age and sex as significant predictors, but histology did not emerge as a significant predictor. This discrepancy could be attributed to the smaller tumor sizes in our study population. The significance of histology reported by previous studies may be further validated in a subsequent multicenter study. In addition, tumor grade reflected the differentiated ability and malignant degree of cancer, which were significantly related to prognosis (37-39). The results of these studies reinforced the reliability of tumor grade in our model. After that, we found that radiotherapy could not provide improved prognosis, which is consistent with the results of the study reported by Zhu *et al.* (40). The prediction of different surgical approaches, including sublobectomy, in N2/3-positive NSCLC is an area that has not been extensively explored in the existing literature. Mao *et al.* reported a nomogram to predict the survival of stage IIIA–N2 NSCLC after surgery, in which this report contains the lobectomy and pneumonectomy, not including other surgical approaches (33). Liang *et al.* also established and validated a novel nomogram that can provide an individual prediction of OS for patients with resected NSCLC, in which surgical approaches involving wedge resection were included for analysis (35). These studies demonstrated that the surgical approaches included significant variables, which may further improve the accuracy and reliability of the prediction of survival benefits for patients with T1N2–3M0 NSCLC.

Nonetheless, it is essential to acknowledge the limitations of our current study. First and foremost, as a retrospective study, there is an inherent risk of population selection bias, and the ability to control for confounding factors may not be as rigorous as in prospective studies. Second, a major limitation arises from the absence of comprehensive information regarding chemotherapy and radiotherapy in the SEER database (41), including details on treatment regimens, courses of chemotherapy, cycles, doses, and radiotherapy methods. Additionally, we could not determine the sequence of chemotherapy and radiotherapy in relation to surgery, which could potentially impact the reliability of our study and the performance of our predictive model. In addition, we could not assess more pretreatment variables which may be related to the survival outcome and the reason why the patients did not receive the surgical treatment, including comorbidity, forced expiratory volume in 1 second (FEV1), diffusing capacity of the lung for carbon monoxide (DLCO), performance score, smoking status, body mass index (BMI), and surgical approach (e.g., video-assisted thoracic surgery or open surgery). Due to our reliance on the SEER database, we were unable to include these parameters in our analysis. Moreover, specific details about LND, including the regions dissected and the number of lymph nodes removed, were not available in the SEER database. Nevertheless, we believe that our study was conducted using clinically relevant factors that are accessible in the SEER database and benefited from a large sample size, offering valuable insights for clinical practice in T1N2–3M0 NSCLC patients. Our findings, particularly regarding the benefits of sublobectomy in stage T1N2–3M0 NSCLC and the visualization of survival advantages associated with different surgical approaches, represent an important contribution. However, to further

validate our results and provide more robust clinical guidance before being recommended for clinical use, prospective large-sample RCTs with comprehensive data on clinicopathological variables, performance status, and detailed treatment regimens should be conducted. These trials would offer a more precise assessment of the outcomes observed in our study and enhance the reliability of clinical recommendations.

Conclusions

Our study demonstrates that surgical intervention could offer significant survival benefits for stage T1N2–3M0 NSCLC patients. Among the surgical approaches, lobectomy emerged as the superior option, providing improved OS and CSS compared to sublobectomy. However, for patients who may not be suitable candidates for lobectomy, sublobectomy may remain a valuable alternative that confers survival advantages. Our predictive model enhances the understanding of the differential benefits associated with various surgical approaches, thus serving as a valuable tool for informing survival discussions between patients and clinicians, guiding the design and monitoring of clinical trials, and facilitating the development of more personalized treatment strategies.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-213/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-213/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-213/coif). The 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).

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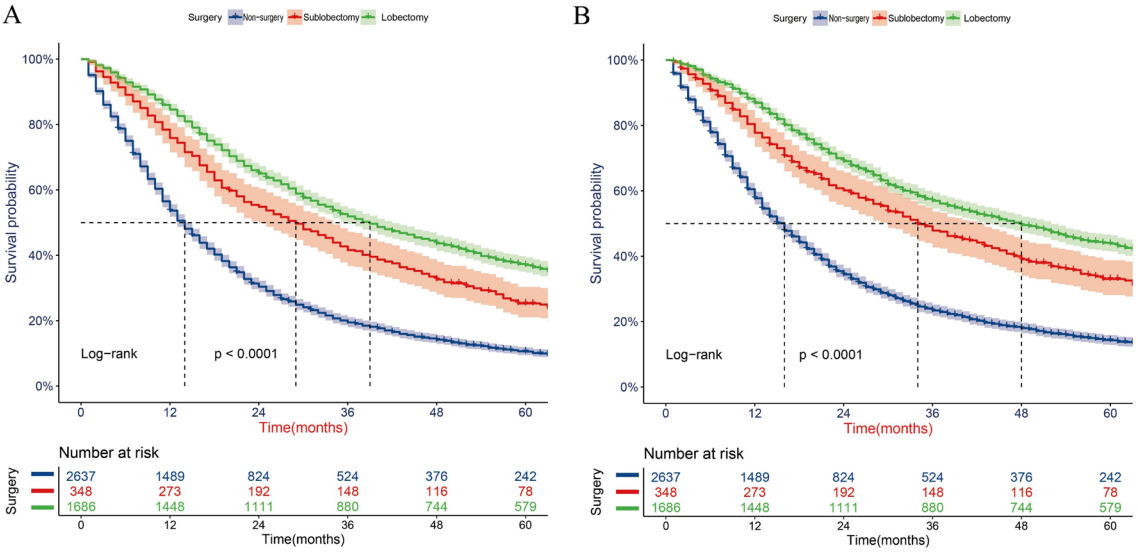

Figure S1 Survival analyses of OS and CSS for T1N2–3M0 NSCLC patients stratified by surgery strategy before PSM. (A) KM curves of OS. (B) KM curves of CSS. OS, overall survival; CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; PSM, propensity score matching; KM, Kaplan-Meier.

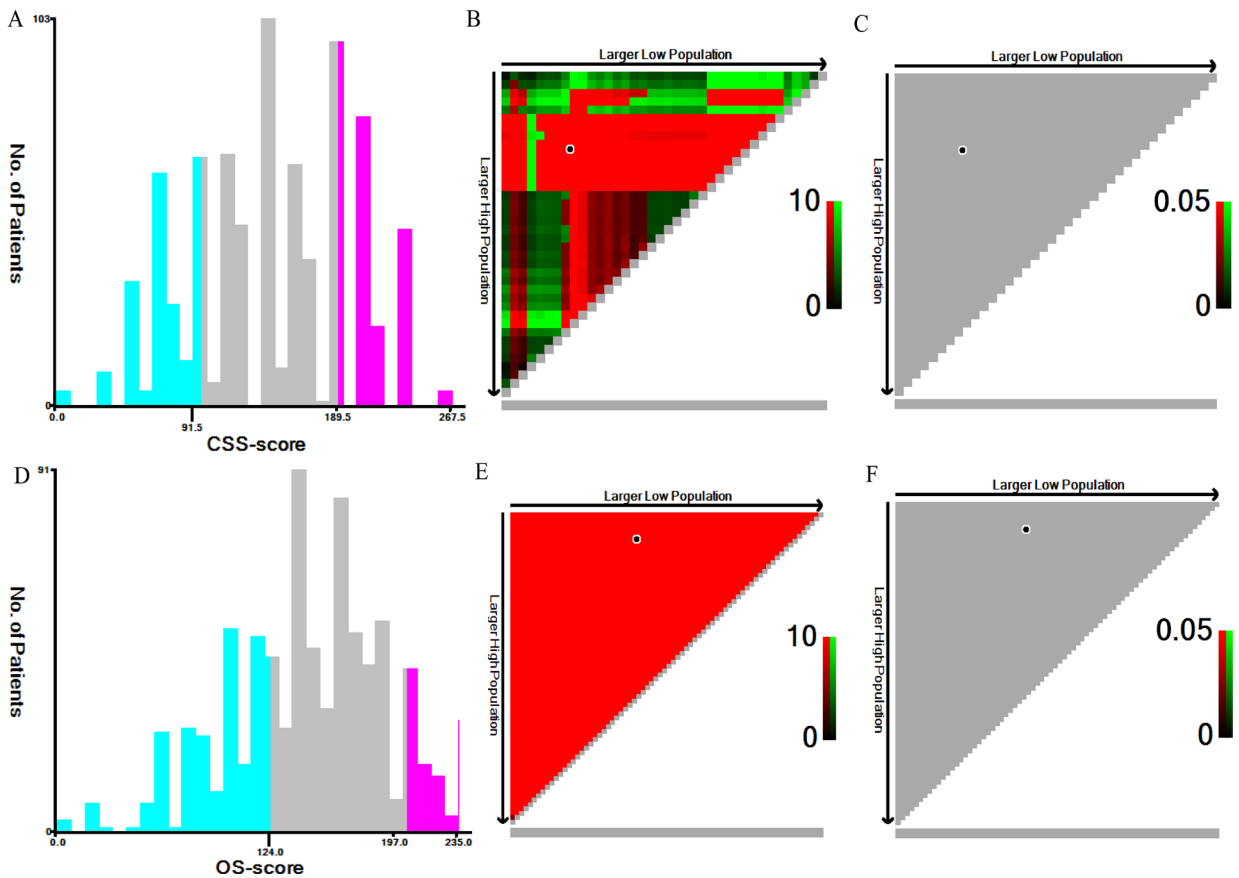

Figure S2 The cut-off value of risk points counted by X-tile based on the nomogram. CSS, cancer-specific survival; OS, overall survival.

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