Development and validation of web-based dynamic nomograms predictive of disease-free and overall survival in patients who underwent pneumonectomy for primary lung cancer

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Background. The tumour-node-metastasis (TNM) staging system is insufficient to precisely distinguish the long-term survival of patients who underwent pneumonectomy for primary lung cancer. Therefore, this study sought to identify determinants of disease-free (DFS) and overall survival (OS) for incorporation into web-based dynamic nomograms.

Methods. The clinicopathological variables, surgical methods and follow-up information of 1,261 consecutive patients who underwent pneumonectomy for primary lung cancer between January 2008 and December 2018 at Sun Yat-sen University Cancer Center were collected. Nomograms for predicting DFS and OS were built based on the significantly independent predictors identified in the training cohort (n = 1009) and then were tested on the validation cohort (n = 252). The concordance index (C-index) and time-independent area under the receiver-operator characteristic curve (AUC) assessed the nomogram's discrimination accuracy. Decision curve analysis (DCA) was applied to evaluate the clinical utility.

Results. During a median follow-up time of 40.5 months, disease recurrence and death were observed in 446 (35.4%) and 665 (52.7%) patients in the whole cohort, respectively. In the training cohort, a higher C-reactive protein to albumin ratio, intrapericardial pulmonary artery ligation, lymph node metastasis, and adjuvant therapy were significantly correlated with a higher risk for disease recurrence; similarly, the independent predictors for worse OS were intrapericardial pulmonary artery and vein ligation, higher T stage, lymph node metastasis, and no adjuvant therapy. In the validation cohort, the integrated DFS and OS nomograms showed well-fitted calibration curves and yielded good discrimination powers with C-index of 0.667 (95% confidence intervals [CIs]: 0.610-0.724) and 0.697 (95% CIs: 0.649-0.745), respectively. Moreover, the AUCs for 1-year, 3-year, and 5-year DFS were 0.655, 0.726, and 0.735, respectively, and those for 3-year, 5-year, and 10-year OS were 0.741, 0.765, and 0.709, respectively. DCA demonstrated that our nomograms could bring more net benefit than the TNM staging system.

Conclusions. Although pneumonectomy for primary lung cancer has brought encouraging long-term out<u>comes, the constructed prediction models could</u> assist in precisely identifying patients at high risk and PeerJ reviewing PDF | (2023:05:86209:0:1:NEW 25 May 2023)



developing personalized treatment strategies to further improve survival.

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- 20

21 Abstract

22 Background. The tumour-node-metastasis (TNM) staging system is insufficient to precisely

- distinguish the long-term survival of patients who underwent pneumonectomy for primary lungcancer. Therefore, this study sought to identify determinants of disease-free (DFS) and overall
- survival (OS) for incorporation into web-based dynamic nomograms.
- 26 Methods. The clinicopathological variables, surgical methods and follow-up information of 1,261
- 27 consecutive patients who underwent pneumonectomy for primary lung cancer between January
- 28 2008 and December 2018 at Sun Yat-sen University Cancer Center were collected. Nomograms
- 29 for predicting DFS and OS were built based on the significantly independent predictors identified
- in the training cohort (n = 1009) and then were tested on the validation cohort (n = 252). The concordance index (C-index) and time-independent area under the receiver-operator characteristic
- curve (AUC) assessed the nomogram's discrimination accuracy. Decision curve analysis (DCA)
- 33 was applied to evaluate the clinical utility.
- 34 **Results.** During a median follow-up time of 40.5 months, disease recurrence and death were
- observed in 446 (35.4%) and 665 (52.7%) patients in the whole cohort, respectively. In the training
- 36 cohort, a higher C-reactive protein to albumin ratio, intrapericardial pulmonary artery ligation,
- 37 lymph node metastasis, and adjuvant therapy were significantly correlated with a higher risk for
- 38 disease recurrence; similarly, the independent predictors for worse OS were intrapericardial
- 39 pulmonary artery and vein ligation, higher T stage, lymph node metastasis, and no adjuvant
- 40 therapy. In the validation cohort, the integrated DFS and OS nomograms showed well-fitted
- 41 calibration curves and yielded good discrimination powers with C-index of 0.667 (95% confidence

- 42 intervals [CIs]: 0.610-0.724) and 0.697 (95% CIs: 0.649-0.745), respectively. Moreover, the AUCs
- 43 for 1-year, 3-year, and 5-year DFS were 0.655, 0.726, and 0.735, respectively, and those for 3-
- 44 year, 5-year, and 10-year OS were 0.741, 0.765, and 0.709, respectively. DCA demonstrated that
- 45 our nomograms could bring more net benefit than the TNM staging system.
- 46 Conclusions. Although pneumonectomy for primary lung cancer has brought encouraging long-
- 47 term outcomes, the constructed prediction models could assist in precisely identifying patients at
- 48 high risk and developing personalized treatment strategies to further improve survival.
- 49
- 50 Keywords pneumonectomy; lung cancer; disease-free survival; overall survival; nomogram
- 51

52 **Introduction**

A multimodality treatment strategy with pneumonectomy is reserved for lung cancer patients in 53 whom tumours invade the main bronchus, pulmonary vessels, or ipsilateral lobe(s) to achieve 54 prolonged survival (Ettinger et al. 2021; Yu et al. 2021). Although reports based on the 55 Surveillance, Epidemiology, and End Results (SEER) program and the National Cancer Database 56 (NCDB) show an apparent decrease in the proportion of pneumonectomies for the surgical 57 treatment of lung cancer over the past twenty years, the constitute ratio remains at 5-10% (Hancock 58 59 et al. 2014; Yu et al. 2021). However, due to the high perioperative morbidity and mortality, reduced lung function, and poor quality-of-life, the long-term survival rate after pneumonectomy 60 remains unsatisfactory and varies (10.8-66.0%) (Dickhoff et al. 2016; Hancock et al. 2014; 61 Herskovic et al. 2017; Yu et al. 2021). Despite many studies that have identified predictive factors 62 for postpneumonectomy survival, the ultimate aims of these studies were principally limited to the 63 confirmation of an isolated clinicopathological feature as a predictor (Rivera et al. 2014; Tabutin 64 65 et al. 2012). The anatomy-based tumour-node-metastasis (TNM) staging is the most widely used model for risk stratification and survival prediction of patients with lung cancer; nevertheless, 66 recent studies have demonstrated that the current staging system is not sufficient to precisely 67 distinguish the long-term survival of patients who underwent pneumonectomy for lung cancer 68 (Dickhoff et al. 2016; Herskovic et al. 2017; Tabutin et al. 2012). Therefore, individualized 69 postpneumoneuctomy management continues to be a challenge for thoracic surgeons. 70

71 A nomogram is a pictorial depiction that can be used to generate a numerical risk probability of a specific clinical outcome (such as complication, recurrence, and death) (Balachandran et al. 72 2015). Therefore, the clinical use of a nonogram that is tailored to the determinate prognostic 73 variables of an individual patient can facilitate a personalized follow-up schedule and a 74 multimodality treatment strategy in oncology (Liu et al. 2020). In addition, a web-based calculator 75 that is transferred from the nomogram can provide a more intuitive and convenient interface to 76 77 assist in communication with patients (Amar et al. 2019). Although several nomograms to predict the prognosis of patients with lung cancer were established in previous studies, an exclusive and 78 online nomogram for this specific population with removal of an entire lung has not yet been 79 available in clinical practice. 80

Therefore, we performed the present study based on a real-world cohort analysis with the aim of identifying the independent clinicopathological variables that predict disease-free and overall

survival (DFS and OS) in patients who underwent pneumonectomy for primary pulmonary malignancy. Moreover, web-based servers according to the integrated nomogram models have

been developed and are freely available for thoracic surgeons to input the predictive variables

required for the individualized DFS and OS probability.

87

88 Materials and Methods

89 Patient Population

Clinical, pathological, surgical, and follow-up information of patients who underwent one-sided 90 pneumonectomy with curative intent for primary lung cancer between January 2008 and December 91 2018 was extracted from the medical records at Sun Yat-sen University Cancer Center. 92 93 Pathological TNM staging was reclassified on the basis of the American Joint Committee on Cancer (AJCC) TNM Staging Manual, 8th Edition. Patients who were less than 18 years of age at 94 surgery, who had other malignant tumours diagnosed before or after pneumonectomy, positive 95 margins, who had follow-up times less than 1 month, and who had unknown surveillance outcomes 96 were excluded. A total of 1261 consecutive patients were enrolled in this study (Figure S1). Then, 97 by generating a random seed (131) with the aid of the R package "Caret", the patients were divided 98 into a training cohort (n=1009) and a validation cohort (n=252) at a proportion of 8:2. 99

100

101 Follow-up Strategy and Endpoints

After undergoing pneumonectomy or completing adjuvant therapy, the patients were routinely 102 followed up with chest computed tomography (CT) enhancement scans plus cervical and 103 abdominal ultrasonography every 3-6 months in the first 3 years, every 6 months at the 4th to 5th 104 years, and annually thereafter until recurrence or death occurred. To reduce the missing data rate, 105 106 telephone, letter, or e-mail consultations and smartphone application surveys were selected as supplements for the outpatient follow-up. All intrathoracic and/or regional recurrence was 107 confirmed by pathology. Distant metastasis was generally diagnosed based on radiology, such as 108 CT, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), 109 or positron emission tomography (PET). 110

- DFS time was calculated from the date of pneumonectomy to the date of disease recurrence, death from noncancer causes, or the last date of follow-up (December 31, 2020). OS time was defined as the interval between pneumonectomy and death from any cause or the last follow-up. The patients who had not met the abovementioned endpoints were recorded as censored cases.
- 115
- 116 Ethics Statement

The institutional ethics committee at Sun Yat-sen University Cancer Center approved thisretrospective study (No. B2022-011-01). All patients signed informed consent before surgery.

- 119
- 120 Statistical Analysis
- 121 To analyse the differences between the training and validation cohorts, categorical variables were
- 122 compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using
- 123 Student's t test or the Mann-Whitney U test, as appropriate. For the survival analyses, based on

the best cut-off values generated by X-tile software (Version 3.6.1, Yale University), the 124 continuous variables of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), 125 and C-reactive protein to albumin ratio (CAR) were transformed into categorical variables. The 126 Kaplan-Meier method was used to screen the priori predictors that were significantly associated 127 128 with DFS and OS in the training cohort. Then, the above significant variables were entered into the least absolute shrinkage and selection operator (LASSO) regression model to further select the 129 most useful prognostic variables with the aid of the minimum lambda (λ). The R package "glmnet" 130 was used to perform the LASSO regression. Subsequently, the clinicopathological variables 131 selected by the LASSO regression were retained in the final Cox proportional hazards model to 132 determine the independent predictors for survival. All statistical analyses were performed by 133 134 Statistical Product and Service Solutions version 23.0 software (SPSS, IBM, Inc., Chicago, IL, USA), and a *P* value less than 0.05 was defined as a significant difference. 135

The independent predictors for DFS and OS that were identified by the aforementioned Cox proportional hazards models in the training cohort were included to generate two nomograms that were formulated using the R package "rms". A calibration plot was used to estimate the calibration between the actual survival probability and the nomogram estimated survival probability. The discrimination was assessed using the area under the curve (AUC) of a receiver-operator characteristic (ROC) curve.

142

143 **Results**

144 Patient Characteristics

In total, 1,370 consecutive patients who underwent one-sided whole lung removal for primary lung cancer between 2008 and 2018 were identified, and 1,261patients met the inclusion criteria and

- 147 were included in this study. Although the annual cases of pneumonectomy remained stable over
- the past ten years (median: 121, range: 94-129), the constitute ratio of pneumonectomy in the surgical treatment of lung cancer decreased steadily from 13.4% in 2008 to 2.5% in 2018 (P < 0.001).
- 151 The patients' median age at diagnosis was 57.4 years (range 20-77 years), and most of the patients
- 152 (86.4%) were male. In all, 131 patients (10.4%) were treated with induction therapy, including 1
- 153 with radiotherapy alone, 8 with concurrent chemoradiotherapy, 10 with immunotherapy alone, and
- 154 112 with chemotherapy alone. In addition, postoperative adjuvant therapy was immunotherapy
- alone in 3 patients, targeted therapy in 4 patients, radiotherapy alone in 15 patients, concurrent
- 156 chemoradiotherapy in 45 patients, and chemotherapy alone in 530 patients. The majority of the
- 157 pneumonectomies (71.1%) were due to primary squamous cell carcinoma, followed by
- adenocarcinoma (17.5%), neuroendocrine tumour (4.6%), and adenosquamous carcinoma (2.5%).
- 159 A minority (18.5%) of the primary tumours were located in the right lung. Pneumonectomy via an
- 160 open approach, three-port video-assisted thoracoscopic surgery (VATS) and uniportal VATS was
- 161 performed in 1225 patients (97.1%), 19 (1.5%) and 17 patients (1.3%), respectively. According to
- the postoperative pathological examination, the constituent ratios of stage 0-I, II, IIIA and IIIB-IV
- 163 were 9.7%, 33.7%, 38.6% and 18.0%, respectively.
- 164 Table 1 lists that characteristics of the training and validation cohort patients were similar.

165

166 Follow-up Results

Twenty-seven patients (2.1%) experienced nononcologic mortality within 90 days after the operation, and the 30-day mortality was 1.4% (18 patients). With a median follow-up time of 40.5 months (range: 1.0-153.1 months), tumour recurrence was observed in 446 patients, and 665 patients experienced death events. The estimated median OS and DFS times for all the patients were 60.9 and 77.6 months, respectively. Moreover, the 5-year OS and DFS rates between the training and validation cohorts were not different (52.1% vs. 49.5%, P= 0.893; and 66.2% vs. 65.9%, P=0.821; respectively).

- 174
- 175 Risk factors and predictive nomogram for disease-free survival
- 176 According to the univariate analysis for DFS in the training cohort (Table 2), higher CAR (versus
- 177 ≤ 0.01 ; P<0.001), intrapericardial pulmonary artery or vein disconnection (versus

extrapericardium; all P<0.001), adenocarcinoma (versus squamous cell carcinoma, SCC; P<0.001), higher T stage (P=0.008), lymph node metastasis (versus N0; P<0.001), and adjuvant therapy (versus no adjuvant therapy; P<0.001) all correlated with a higher risk for disease recurrence. After LASSO-Cox regression to further reduce possible redundancy (Figure 1A and 1B), CAR, pulmonary artery disconnection, N stage, and adjuvant therapy remained significant indicators of DFS (Table 3) and were used to build the final nomogram model (Figure 2A).

- Calibration was depicted by drawing the plots of the predicted 1-year, 3-year, and 5-year DFS rates 184 with the confidence intervals (CIs) from the nomogram versus the actual probabilities in the 185 training (Figure 3A, 3B, 3C) and validation cohorts (Figure 3D, 3E, 3F). The nomogram showed 186 187 good predictive discrimination with a concordance index (c-index) of 0.647 (95% CIs: 0.632-0.662) in the training cohort and 0.667 (95% CIs: 0.610-0.724) in the validation cohort, 188 respectively. Additionally, the AUCs for the 1-year, 3-year, and 5-year DFS generated via 189 bootstrap resampling were 0.659, 0.685, and 0.694, respectively, denoting that the model was not 190 overfitted (Figure 4A, 4B, 4C). The external validation for the 1-year, 3-year, and 5-year DFS 191 showed AUCs of 0.655, 0.726, and 0.735, respectively, demonstrating the model's good 192 discrimination (Figure 4D, 4E, 4F). 193
- For clinical utility, the decision curve analysis (DCA) indicated that using the nomogram model to predict 1-year, 3-year, and 5-year DFS added more net benefit across the reasonable threshold probabilities than the TNM stage in both the training (Figure 5A, 5B, 5C) and validation cohorts (Figure 5D, 5E, 5F).

198

199 Risk factors and predictive nomogram for overall survival

Similarly, through the univariate analysis (Table 2) and the LASSO-Cox proportional hazards regression model (Figure 1C and 1D), intrapericardial pulmonary artery disconnection,

intrapericardial pulmonary vein disconnection, higher T stage, lymph node metastasis, and no

adjuvant therapy were identified as independent risk factors for OS (Table 3). The calibration

curves between the predicted probability of 3-year, 5-year, and 10-year OS and the actual

205 probability also appeared to have excellent consistency (Figure S2). The OS nomogram had a C-

index of 0.675±0.025 in the training cohort and 0.697±0.048 in the validation cohort, reflecting

207 good discrimination. Furthermore, time-dependent ROCs and AUCs at 3 years, 5 years, and 10

208 years were used to validate the prognostic accuracy of the OS nomogram (Figure S3). The DCA

209 indicated that when the threshold probability of a patient or surgeon was greater than 20%, using

our OS nomogram to predict the 3-year, 5-year, and 10-year OS could increase the positive benefit

- 211 more than either the "treat all" scheme, the "treat none" scheme, or the traditional staging system
- in the training (Figure S4A, S4B, S4C) and validation (Figure S4D, S4E, S4F) groups.
- 213

214 Discussion

215 In this single-centre retrospective study, the 30-day and 90-day nononcologic mortality rates of all 1,261 patients after pneumonectomy for primary lung cancer were 1.4% and 2.1%, respectively, 216 and the estimated 5-year OS and DFS rates of the whole cohort were 51.6% and 66.1%, 217 respectively. A total of 24 variables, including routine clinical, pathological, staging and treatment 218 information, were included to select significant risk factors through Kaplan-Meier univariate 219 analysis and further LASSO-Cox multivariate analysis. Then, DFS and OS nomogram models 220 were developed to predict individualized survival probabilities. In the training and validation 221 222 cohorts, all of the models calibrated well and demonstrated good to moderate predictive discrimination. In addition, our for risk stratification models could bring more clinical benefit than 223 the traditional TNM staging system. Most importantly, the web interactive calculators can be freely 224 https://thoracicsurgery-nccchina.shinyapps.io/Disease-free-survival/ used at and 225 https://thoracicsurgery-nccchina.shinyapps.io/Overall-survival/. By inputting the easy-to-226 available predictive variables (Figure 6), individualized prediction of survival plot and probability 227 228 (with 95% CIs) would assist thoracic surgeons or patients in making clinical decisions.

With the aid of the National Medicare Claims Database and the Nationwide Inpatient Sample, 229 John D. Birkmeyer et al. reported that the adjusted postpneumonectomy mortality rates in very 230 high-volume hospitals (average no. of pneumonectomy/year > 46 cases) were significantly lower 231 than those in very low-volume hospitals (< 9 cases) (Birkmeyer et al. 2002). In our division, the 232 annual cases of pneumonectomy remained stable over the past decade (median: 121, range: 94-233 234 129), which was more than that in any other report; therefore, plenty of clinical experience in preoperative (induction therapy, nutrition support, etc.), intraoperative (pulmonary artery pressure 235 [PAP] and central venous pressure [CVP] monitoring, bronchial stump coverage or reinforcement, 236 etc.) and postoperative management (liquid volume control, cardioversion, enhanced recovery 237 after surgery, adjuvant therapy, etc.) were accumulated to reduce postoperative complications. 238 Correspondingly, the 30-day and 90-day nononcologic mortality rates in this present large cohort 239 240 were lower than those of previous studies (30-day mortality: 0-26.0%; 90-day mortality: 3.0-21.0%) (Brunswicker et al. 2022; Tabutin et al. 2012; Yu et al. 2021; Yun et al. 2022). Moreover, 241 the long-term outcome was higher than that in the population-based analysis(Yu et al. 2021) and 242 was consistent with that in more recently published results(Brunswicker et al. 2022; Yun et al. 243 2022). 244

245 Primary tumour and/or metastatic lymph node invasion of pulmonary vessels and/or

246 pericardium could provoke the spread of tumour cells (TCs) into the peripheral blood circulation,

which leads to early distant metastasis and potential micrometastasis after surgery (Wei et al. 2019).

Numerous studies have revealed that patients with main vessel or pericardium invasion had worse 248 survival than patients with the same TNM staging(Rami-Porta et al. 2015; Wei et al. 2019). 15.2% 249 250 of patients in the current study, enough lengths could not be separated or the safety margins could not be ensured of the main pulmonary artery and/or vein due to invasion into the main pulmonary 251 vessels and/or pericardium, and intrapericardial pneumonectomy was carried out. Consistent with 252 other studies, intrapericardial ligation of the pulmonary vessels, especially arteries, reflected the 253 potential release of TCs into the bloodstream, and intrapericardial artery ligation was notably 254 associated with earlier disease recurrence and poorer prognosis in the multivariate analysis. A 255 256 randomized clinical trial reported by Lunxu Liu et al. indicated that the ligation of arteries prior to veins during lung cancer surgery was a significant risk factor for increased circulating tumour cells 257 (CTCs) in peripheral blood and was statistically linked to poorer long-term survival(Wei et al. 258 2019). Therefore, the pulmonary vein-first procedure should also be recommended in patients who 259 undergo pneumonectomy (especially intrapericardial pneumonectomy) for primary lung cancer to 260 reduce the risk of TCs directly entering the systemic circulation. In addition, surgical manipulation 261 may cause the haematogenic dissemination of TCs, and therefore, no-touch isolation techniques 262 263 should be reinforced during pneumonectomy to avoid potential iatrogenic TCs shedding(Wei et

264 al. 2019).

Whether lung cancer patients after pneumonectomy can tolerant and benefit from adjuvant 265 treatment is another controversial issue. A French multicentre retrospective study enrolled 1,466 266 patients who underwent pneumonectomy for non-small cell lung cancer (NSCLC) and reported 267 that adjuvant treatment had no impact on long-term outcome(Riquet et al. 2014). In contrast, our 268 269 present study suggested that postpneumonectomy treatment could significantly improve long-term survival; nevertheless, postpneumonectomy treatment due to advanced staging did not change the 270 high recurrence rate. The cause of the different effects of postpneumonectomy treatment on 271 survival and recurrence in this real-world cohort study was speculated to be that chemotherapy 272 alone was selected as the main postpneumonectomy treatment regimen in most of the patients (530 273 of 544 patients, 88.8%). Postoperative chemotherapy can effectively prevent distant metastasis and 274 275 thereby prolong the survival period in patients with NSCLC(Pignon et al. 2008); however, postoperative concurrent radiotherapy can simultaneously reduce local recurrence risk (Hui et al. 276 2021). Similarly, Zhouguang Hui et al. also recently reported that, compared with postoperative 277 chemotherapy alone, concurrent chemoradiotherapy for patients with pIII(N2) NSCLC after 278 pneumonectomy could not only significantly reduce local recurrence and distant metastasis, but 279 also improve DFS and OS(Wang et al. 2019). Therefore, we support that postpneumonectomy 280 concurrent chemoradiotherapy should be recommended for locally advanced NSCLC patients who 281 went through the perioperative period safely. 282

Compared with published studies regarding the prognosis of pneumonectomy(Brunswicker et al. 2022; Riquet et al. 2014; Rivera et al. 2014; Tabutin et al. 2012; Wang et al. 2019), there were four main advantages in the present study. First, this retrospective study was carried out based on a larger single-centre cohort, thus ensuring more homogenous diagnosis, treatment, and

perioperative management. Second, almost all clinical, pathological, staging and treatment 287 variables were included to screen for prognostic factors. Moreover, the LASSO regression model 288 was applied for further predictor selection, and this model is less likely to be overfitted and can be 289 more accurate than stepwise selection in the Cox proportional hazards model. Third, to our 290 291 knowledge, this is the first integrated nomogram specifically for patients who underwent pneumonectomy for primary lung cancer to estimate prognosis. Fourth, the pictorial nomogram is 292 contained in a website-based calculator, where easy-to-available variables are entered into and the 293 likelihood of personalized survival is computed. We should acknowledge that the retrospective 294 nature of our study inevitably resulted in several limitations. First, some patients were excluded as 295 a result of missing data (e.g., follow-up outcome), which may bring potential selection bias. 296 297 Second, the time span of this retrospective cohort study was 11 years. During that period, the surgical techniques (robot-assisted thoracic surgery, sleeve lobectomy, etc.), incision methods 298 (uniport and subxiphoid VATS, etc.), neoadjuvant (immunotherapy plus chemotherapy, targeted 299 therapy, etc.) and adjuvant strategies (targeted therapy, immunotherapy, etc.), and the use of liquid 300 biopsy for therapy monitoring (CTCs, minimal residual disease, etc.) had changed dramatically. 301 and therefore, potential selection bias and follow-up bias were unavoidable. In addition, the 302 nomogram was developed based on the supposition that all future endpoint events would be 303 304 identical to the time of the patient enrolment; in other words, the predictive variables and accuracy of a nomogram were not to updated over time. Moreover, our nomograms were built and validated 305 using single-centre data, and thus, whether the two nomograms can be universally used remains to 306 be determined by validating it in an external population or a prospective cohort. 307

308 309

310 **Conclusions**

In summary, we built two web-based interactive nomograms with good calibration and discrimination for individually predicting the DFS and OS of patients who underwent pneumonectomy for primary lung cancer. Moreover, our nomograms used for risk stratification could not only add clinical benefit to the traditional TNM classification system, but could also assist thoracic surgeons or patients in making personalized therapeutic recommendations and follow-up regimens.

317

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321

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326 **Conflicts of Interest**

327 The authors have no conflicts of interest or financial ties to disclose.

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400

Table 1(on next page)

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1 Table 1 Clinical, pathological, and surgical characteristics of patient who underwent pneumonectomy for

2 primary lung cancer in the overall, training, and validation cohorts.

	Overall	Training cohort	Validation cohort	Р
Characteristic	(N = 1261)	(N = 1009)	(N = 252)	value
Year of operation, n (%)				
2008-2011	455 (36.0%)	356 (35.3%)	99 (39.3%)	
2012-2015	466 (37.0%)	376 (37.3%)	90 (35.7%)	0.478
2016-2018	340 (27.0%)	277 (27.5%)	63 (25.0%)	
Mean age at diagnosis, years	57 4 (20 77)	57 4 (20 77)	572()	0.850
(range)	37.4 (20-77)	37.4 (20-77)	37.5 (-)	0.839
Sex, n (%)				
Female	171 (13.6%)	140 (13.9%)	31 (12.3%)	0.514
Male	1090 (86.4%)	869 (86.1%)	221 (87.7%)	0.314
Mean duration of chief complaint,	3 3 (0 08 48 0)	3 3 (0.08 48 0)	32(01360)	0 707
months (range)	5.5 (0.08-48.0)	5.5 (0.08-48.0)	5.2 (0.1-50.0)	0.707
Smoking history, n (%)				
Yes	1028 (81.5%)	823 (81.6%)	205 (81.3%)	0.937
No	233 (18.5%)	186 (18.4%)	47 (18.7%)	0.757
Mean BMI, kg/m ² (range)	23.8 (14.2-36.5)	23.7 (14.2-36.5)	24.2 (-)	0.028
Median weight loss in	0.0(0.0-15.0)	0.0.(0.0-15.0)	0.0.(0.0-10.0)	0 1 2 3
preoperative 3 months, kg (range)	0.0 (0.0-15.0)	0.0 (0.0-15.0)	0.0 (0.0-10.0)	0.125
Induction therapy, n (%)				
Yes	131 (10.4%)	104 (10.3%)	27 (10.7%)	0.850
No	1130 (89.6%)	905 (89.7%)	225 (89.3%)	0.050
Mean FEV1, (range)	2.21 (0.77-3.99)	2.21 (0.77-3.98)	2.20 (0.92-3.99)	0.692
Mean FEV1 %pred, % (range)	72.4 (26.7-127.6)	72.7 (26.7-118.0)	71.4 (30.0-127.6)	0.286
Mean DLCO, (range)	7.07 (1.33-32.88)	7.05 (1.33-17.39)	7.16 (2.38-32.88)	0.465
Mean DLCO %pred, % (range)	78.0 (1.4-359.0)	77.9 (1.4-197.0)	78.5 (31.0-359.0)	0.711
Median NLR, (range)	2.43 (0.25-65.87)	2.46 (0.25-65.87)	2.71 (0.59-11.17)	0.004
Mean PLR, (range)	148.30 (16.35-	149.03 (16.35-	145.47 (50.53-	0 510
	1264.52)	1264.52)	500.00)	0.010
Median CAR, (range)	0.00 (0.00-0.93)	0.00 (0.00-0.84)	0.00 (0.00-0.93)	0.338
Incision method, n (%)				
Open	1225 (97.1%)	978 (96.9%)	247 (98.0%)	
Uniportal VATS	17 (1.3%)	14 (1.4%)	3 (1.2%)	0.564
Three-portal VATS	19 (1.5%)	17 (1.7%)	2 (0.8%)	
Disconnection of pulmonary				
artery, n (%)				
Intrapericardium	180 (14.3%)	144 (14.3%)	36 (14.3%)	0 995
Extra-pericardium	1081 (85.7%)	865 (85.7%)	216 (85.7%)	0.770
Disconnection of pulmonary vein,				

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n (%)				
Intrapericardium	226 (17.9%)	181 (17.9%)	45 (17.9%)	0.076
Extra-pericardium	1035 (82.1%)	828 (82.1%)	207 (82.1%)	0.970
Disconnection of main bronchus,				
n (%)				
Stapler	1238 (98.2%)	992 (98.3%)	246 (97.6%)	0.460
Manual suture	23 (1.8%)	17 (1.7%)	6 (2.4%)	0.400
Pathology, n (%)				
Squamous cell carcinoma	897 (71.1%)	722 (71.6%)	175 (69.4%)	
Adenocarcinoma	221 (17.5%)	175 (17.3%)	46 (18.3%)	
Adenosquamous carcinoma	31 (2.5%)	24 (2.4%)	7 (2.8%)	0.970
Neuroendocrine Tumor	58 (4.6%)	46 (4.6%)	12 (4.8%)	
Other	54 (4.3%)	42 (4.2%)	12 (4.8%)	
Grade, n (%)				
Well	70 (5.6%)	52 (5.2%)	18 (7.1%)	
Moderately	632 (50.1%)	506 (50.1%)	126 (50.0%)	0.451
Poorly	559 (44.3%)	451 (44.7%)	108 (42.9%)	
Mean tumor size, cm (range)	4.7 (0.0-22.0)	4.7 (0.2-22.0)	4.6 (0.0-15.0)	0.447
Pathological T stage, n (%)				
T0-1	100 (7.9%)	83 (8.2%)	17 (6.7%)	
T2	562 (44.6%)	449 (44.5%)	113 (44.8%)	0.580
Т3	406 (32.2%)	318 (31.5%)	88 (34.9%)	0.380
T4	193 (15.3%)	159 (15.8%)	34 (13.5%)	
Pathological N stage, n (%)				
N0	262 (20.8%)	205 (20.3%)	57 (22.6%)	
N1	580 (46.0%)	476 (47.2%)	104 (41.3%)	0.243
N2	419 (33.2%)	328 (32.5%)	91 (36.1%)	
Pathological TNM stage, n (%)				
0-I	122 (9.7%)	97 (9.6%)	25 (9.9%)	
II	425 (33.7%)	342 (33.9%)	83 (32.9%)	0.917
IIIA	487 (38.6%)	392 (38.9%)	95 (37.7%)	0.717
IIIB-IV	227 (18.0%)	178 (17.6%)	49 (19.4%)	
Adjuvant therapy, n (%)				
Yes	597 (47.3%)	465 (46.1%)	132 (52.4%)	0.073
No	664 (52.7%)	544 (53.9%)	120 (47.6%)	0.075
Laterality, n (%)				
Right	233 (18.5%)	193 (19.1%)	40 (15.9%)	0.234
Left	1028 (81.5%)	816 (80.9%)	212 (84.1%)	0.234
30-day mortality, n (%)	18 (1.4%)	12 (1.2%)	6 (2.4%)	0.154
90-day mortality, n (%)	27 (2.1%)	20 (2.0%)	7 (2.8%)	0.435
5-year DFS rate (%)	66.1%	66.2%	65.9%	0.821

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_	5-year OS rate (%)	51.6%	52.1%	49.5%	0.893
3	Abbreviations: BMI, body mass index;	FEV1, forced expirat	ory volume in 1 second	l; DLCO, carbon n	nonoxide
4	diffusing capacity; NLR, neutrophil to	lymphocyte ratio; PL	R, platelet to lymphod	yte ratio; CAR, C	-reactive
5	protein to albumin ratio; VATS, video	-assisted thoracoscop	ic surgery; TNM: tum	our-node-metastas	is; DFS:
6	disease-free survival; OS: overall surviv	val.			
7					

8 Table 2 The Kaplan-Meier analyses of prognostic predictors of disease-free survival and overall survival.

Charactoristia	$N_{\alpha}(0/)$	Disease-free surv	vival	Overall surviv	val
Characteristic	NO. (70)	5-year DFS rate (%)	P value	Overall survival 5-year OS rate (%) P value 53.3% 0.419 50.5% 0.719 52.4% 0.719 52.1% 0.059 53.4% 0.059 53.4% 0.059 52.3% 0.710 52.3% 0.710 51.3% 0.141 53.1% 0.141 53.1% 0.030 42.5% 0.030 48.7%	
Age at diagnosis, years					
< 60	584 (57.9%)	60.2%	0.402	53.3%	0.410
≥ 60	425 (42.1%)	57.0%	0.402	50.5%	0.419
Sex					
Female	140 (13.9%)	53.7%	0.246	52.4%	0.710
Male	869 (86.1%)	59.8%	0.240	52.1%	0.719
Duration of chief					
complaint, months					
≤ 1	400 (39.6%)	57.6%		53.4%	
1-3	321 (31.8%)	59.4%	0.700	48.3%	0.059
> 3	288 (28.6%)	60.2%		54.9%	
Smoking history					
Yes	823 (81.6%)	59.6%	0.224	52.3%	0.710
No	186 (18.4%)	56.3%	0.234	51.3%	0.710
BMI, kg/m ²					
≤ 18.4	37 (3.7%)	47.4%		44.6%	
18.5-23.9	519 (51.4%)	60.9%	0.710	51.9%	0.141
\geq 24.0	453 (44.9%)	57.5%		53.1%	
Weight loss in					
preoperative 3 months					
Yes	174 (17.2%)	57.2%	0 548	42.5%	0.030
No	835 (82.8%)	59.3%	0.540	54.1%	0.050
Induction therapy					
Yes	104 (10.3%)	53.7%	0 233	48.7%	0.418
No	905 (89.7%)	59.6%	0.255	52.4%	0.410
FEV1 %pred					
$\geq 80\%$	329 (32.6%)	59.6%		55.9%	
50-79%	592 (58.7%)	59.1%	0.895	51.5%	0.043
<50%	88 (8.7%)	54.1%		40.9%	
DLCO %pred					
$\geq 80\%$	422 (41.8%)	60.3%	0.802	56.7%	0.008
60-79%	402 (39.8%)	58.2%	0.002	51.7%	0.000

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< 600/	105 (10 40/)	57 70/		42 20/	
< 00%	185 (18.4%)	57.7%		43.3%	
NLR	957 (94 00/)	50 40/		52.00/	
≥ 4.28	837 (84.9%)	59.4%	0.250	33.9%	0.003
> 4.28	152 (15.1%)	56.2%		40.9%	
PLK	000 (00 10/)	50.20/		52.00/	
≤ 220.85	909 (90.1%)	59.3%	0.235	55.9% 22.7%	< 0.001
> 220.85	100 (9.9%)	55.2%		33.1%	
	5(0)(5(20/)	(2, 20)		56.00/	
≤ 0.01	568 (56.3%)	63.2%	< 0.001	56.8%	0.005
> 0.01	441 (43.7%)	53.6%		45.4%	
Incision method		50.50/		51.00/	
Open	978 (96.9%)	58.5%	0.050	51.3%	0.015
Uniportal VAIS	14 (1.4%)	85.7%	0.273	92.9%	0.017
Three-portal VATS	17 (1.7%)	63.7%		75.5%	
Disconnection of					
pulmonary artery					
Intrapericardium	144 (14.3%)	41.6%	< 0.001	29.3%	< 0.001
Extra-pericardium	865 (85.7%)	61.5%		56.1%	
Disconnection of					
pulmonary vein					
Intrapericardium	181 (17.9%)	44.3%	< 0.001	31.9%	< 0.001
Extra-pericardium	828 (82.1%)	61.7%		56.6%	
Disconnection of main					
bronchus					
Stapler	992 (98.3%)	59.0%	0 439	52.2%	0 289
Manual suture	17 (1.7%)	55.8%	0.159	48.4%	0.209
Pathology					
Squamous cell carcinoma	722 (71.6%)	62.7%		54.5%	
Adenocarcinoma	175 (17.3%)	42.7%	< 0.001	48.0%	0.017
Other	112 (11.1%)	59.9%		43.4%	
Grade					
Well	52 (5.2%)	71.2%		70.0%	
Moderately	506 (50.1%)	60.2%	0.093	54.7%	< 0.001
Poorly	451 (44.7%)	55.9%		47.1%	
Tumor size, cm					
\leq 3	195 (%)	61.5%		70.0%	
$>3, \le 5$	486 (%)	61.1%	0.074	54.0%	<0.001
$> 5, \le 7$	219 (%)	53.7%	0.074	38.0%	~0.001
> 7	109 (%)	54.6%		41.2%	
Pathological T stage					
T0-1	83 (8.2%)	72.8%	0.008	84.6%	< 0.001

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T2	449 (44.5%)	60.7%		58.1%		
Т3	318 (31.5%)	53.5%		41.7%		
T4	159 (15.8%)	56.9%		41.2%		
Pathological N stage						
N0	205 (20.3%)	72.0%		73.3%		
N1	476 (47.2%)	64.0%	< 0.001	57.5%	< 0.001	
N2	328 (32.5%)	41.1%		31.6%		
Pathological TNM stage						
0-I	97 (9.6%)	70.8%		83.7%		
II	342 (33.9%)	67.5%	<0.001	65.8%	<0.001	
IIIA	392 (38.9%)	56.3%	<0.001	46.4%	<0.001	
IIIB-IV	178 (17.6%)	38.1%		23.8%		
Adjuvant therapy						
No	544 (53.9%)	68.3%	<0.001	48.5%	0.016	
Yes	465 (46.1%)	49.0%	<0.001	56.9%	0.010	
Laterality						
Right	193 (19.1%)	59.4%	0.922	48.7%	0.092	
Left	816 (80.9%)	58.9%	0.832	52.9%	0.082	

9 Abbreviations: DFS: disease-free survival; OS: overall survival; BMI, body mass index; FEV1, forced expiratory

10 volume in 1 second; DLCO, carbon monoxide diffusing capacity; NLR, neutrophil to lymphocyte ratio; PLR,

11 platelet to lymphocyte ratio; CAR, C-reactive protein to albumin ratio; VATS, video-assisted thoracoscopic

12 surgery; TNM: tumour-node-metastasis.

13

14 Table 3 The least absolute shrinkage and selection operator (LASSO)-Cox regression model to further select

15 prognostic predictor of disease-free survival and overall survival.

Characteristic	Disease-free sur	vival	Overall survival			
Characteristic	HR (95% CIs)	P value	HR (95% CIs)	P value		
Weight loss in preoperative 3 months						
No	—		Reference			
Yes	—		1.183 (0.948-1.477)	0.137		
FEV1 %pred						
$\geq 80\%$	—		Reference			
50-79%	—		1.196 (0.977-1.464)	0.082		
<50%	—		1.228 (0.865-1.742)	0.251		
DLCO %pred						
$\geq 80\%$	—		Reference			
60-79%	—		0.949 (0.774-1.163)	0.612		
< 60%	—		1.107 (0.859-1.427)	0.430		
NLR						
\leq 4.28			Reference			
> 4.28	_		1.129 (0.860-1.482)	0.383		

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PLR				
≤ 226.85	_	—	Reference	
> 226.85	_	—	1.255 (0.917-1.720)	0.156
CAR				
≤ 0.01	Reference		Reference	
> 0.01	1.532 (1.237-1.897)	< 0.001	1.186 (0.982-1.432)	0.077
Disconnection of pulmonary artery				
Pericardium	Reference		Reference	
Extra-pericardium	0.633 (0.483-0.828)	0.001	0.717 (0.549-0.937)	0.015
Disconnection of pulmonary vein				
Pericardium	Reference		Reference	
Extra-pericardium	0.772 (0.564-1.055)	0.104	0.747 (0.581-0.960)	0.023
Pathology				
Squamous cell carcinoma	Reference		Reference	
Adenocarcinoma	1.534 (1.175-2.003)	0.002	1.120 (0.880-1.426)	0.356
Other	1.182 (0.837-1.671)	0.342	1.285 (0.981-1.683)	0.068
Grade				
Well	_	—	Reference	
Moderately	_	_	1.517 (0.923-2.493)	0.100
Poorly	_	_	1.708 (1.036-2.815)	0.036
Pathological T stage				
T0-1	Reference		Reference	
T2	1.401 (0.873-2.247)	0.162	2.339 (1.356-4.035)	0.002
T3	1.681 (1.042-2.713)	0.033	3.239 (1.874-5.598)	< 0.001
T4	1.343 (0.800-2.254)	0.264	3.108 (1.750-5.519)	< 0.001
Pathological N stage				
N0	Reference		Reference	
N1	1.262 (0.998-1.747)	0.051	1.679 (1.275-2.212)	< 0.001
N2	2.046 (1.467-2.852)	< 0.001	3.264 (2.462-4.327)	< 0.001
Adjuvant therapy				
No	Reference		Reference	
Yes	1.455 (1.168-1.811)	0.001	0.592 (0.494-0.709)	< 0.001
Abbreviation: HR, hazard ratio; CIs, co	nfidence intervals; FEV1,	forced expir	atory volume in 1 second	d; DLCO,

17 carbon monoxide diffusing capacity; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio;

18 CAR, C-reactive protein to albumin ratio.

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Figure 1 Texture feature selection using the least absolute shrinkage and selection operator (LASSO) regression model. (A) and (C) The LASSO model for the exploration of the features related to DFS and OS used tenfold cross-validation via the minimum crit

Figure 1 Texture feature selection using the least absolute shrinkage and selection operator (LASSO) regression model. (A) and (C) The LASSO model for the exploration of the features related to DFS and OS used tenfold cross-validation via the minimum criteria. (B) For the 8 texture features related to DFS, the LASSO coefficient profiles are shown. (D) For the 14 texture features related to OS, the LASSO coefficient profiles are shown. The vertical line is drawn at the least partial likelihood deviance using tenfold cross-validation.

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Figure 2 Nomogram for predicting DFS and OS among patients who underwent pneumonectomy for primary lung cancer. (A) The sum of the prognostic factor points corresponds to the DFS probability at 1-year, 3-year, and 5-year. (B) The sum of the prognostic fac

Figure 2 Nomogram for predicting DFS and OS among patients who underwent pneumonectomy for primary lung cancer. (A) The sum of the prognostic factor points corresponds to the DFS probability at 1-year, 3-year, and 5-year. (B) The sum of the prognostic factor points corresponds to the OS probability at 3-year, 5-year, and 10-year. CAR: C-reactive protein to albumin ratio.

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Points	0	10		20	30		10	50	60		70	80		90	100
Points							>	0.01							
CAR	≤ 0.01														
Disconnection.of.pulmonary	.artery – Extra-pericar	dium			N1			Perio	ardium						
N.stage	NO											-		_	N2
Adjuvant.threapy	NO							Yes							
Total Points	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280
1-year DFS Probability		0.9)		0.85		0.8	0.	75	0.7	0.65	0.6	0.55	0.5	
3-year DFS Probability	0.85	0.8		0.75	0.7	0.65	0.6	0.55	0.5	0.45	0.4 0	35 0	3 0.2	5 0.2	
5-year DFS Probability	0.8			0.7		0.6	(0.5	0.4		0.3		0.2		
Deinte	0	10		20	30	4	10	50	60		70	80		90	100
Points				Pericard	ium										
Disconnection.of.pulmonary	Extra-pericar	dium		Pericardi	um										
Disconnection.of.pulmonary	.vein Extra-pericar	dium								т2					TA
T.stage	T0-1									12				ТЗ	
N.stage	NO					N1									
Adjuvant.threapy	Ves			_		NO							112		
Total Points			,	, <u>, ,</u>											
3-year OS Probability	0		5	, 		100		150	-,				250		300
5-year OS Probability				0.9		0.8		0.7	0.6	0.5	0.4	0.3	0.2	0.1	
10-year OS Probability		0.9		5.0		0.7	0.6	0.5	0.4	0.3	0.2	0.	1		
		0.8		0.7	0.6	0.5	0.4	0.3	0.2	0.1					

Figure 3 Calibration curves of the nomogram to predict DFS probability at 1-year (A and D), 3-year (B and E), and 5-year (C and F) in the training cohort and validation cohort.

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Figure 4 Receiver-operator characteristic curve testing the power of the nomogram for predicting 1-year (A and D), 3-year (B and E), and 5-year (C and F) DFS probability in the training cohort and validation cohort. AUC: area under the curve.

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Figure 5 Decision curves for the nomogram and the TNM staging system to predict 1year (A and D), 3-year (B and E), and 5-year (C and F) DFS probability in the training cohort and validation cohort. TNM: tumour-node-metastasis.

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Figure 6 The interface of our web-based dynamic nomogram for predicting DFS probability (with 95% CI) among patients who underwent pneumonectomy for primary lung cancer. CAR: C-reactive protein to albumin ratio.

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