



Risk-score model to predict prognosis of malignant airway obstruction after interventional bronchoscopy

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Background: Interventional bronchoscopy exhibits substantial effects for patients with malignant airway obstruction (MAO), while little information is available regarding the potential prognostic factors for these patients.

Methods: Between October 31, 2016, and July 31, 2019, a total of 150 patients undergoing interventional bronchoscopy and histologically-confirmed MAO were collected, in which 112 eligible participants formed the cohort for survival study. External validation cohort from another independent institution comprised 33 MAO patients with therapeutic bronchoscopy. The least absolute shrinkage and selection operator regression (LASSO) was applied to the model development dataset for selecting features correlated with MAO survival for inclusion in the Cox regression from which we elaborated the risk score system. A nomogram algorithm was also utilized.

Results: In our study, we observed a significant decline of stenosis rate after interventional bronchoscopy from 71.7%±2.1% to 36.6%±2.7% ($P<0.001$) and interventional bronchoscopy dilated airway effectively. Patients in our study undergoing interventional bronchoscopy had a median survival time of 614.000 days (95% CI: 269.876–958.124). Patients receiving distinct therapeutic methods of interventional bronchoscopy had different prognosis ($P=0.022$), and patients receiving treatment of electrocoagulation in combination with stenting and electrosurgical snare had worse survival than those receiving other options. Multivariate Cox analysis revealed that nonsmoking status, adenoid cystic carcinoma, and low preoperative stenosis length, as independent predictive factors for better overall survival (OS) of MAO patients. Then, the nomogram based on Cox regression and risk score system based on results from LASSO regression were elaborated respectively. Importantly, this risk score system was proved to have better performance than the nomogram and other single biomarkers such as traditional staging system (area under the curve 0.855 *vs.* 0.392–0.739). Survival curves showed that patients with the higher risk-score had poorer prognosis than

those with lower risk-score (third quantile of OS: 126.000 days, 95% CI: 73.588–178.412 *vs.* 532.000 days, 95% CI: 0.000–1,110.372; $P < 0.001$).

Conclusions: Nonsmoking status, adenoid cystic carcinoma, and low preoperative stenosis length, were independent predictive factors for better OS of MAO patients. We proposed a nomogram and risk score system for survival prediction of MAO patients undergoing interventional bronchoscopy with good performance.

Keywords: Lung cancer; malignant airway obstruction (MAO); therapeutic bronchoscopy; prognostic biomarker; risk score

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Introduction

Malignant airway obstruction (MAO) is often a life-threatening disorder with a 5-year survival rate of 18.5%, due to their debilitating dyspnea and subsequent diseases such as respiratory distress, infection, and bleeding (1). Stridor may occur in tracheobronchial stenosis less than 25% of the luminal diameter (2). The main cause of MAO is lung and esophageal cancers (3). In the course of patients' illness, thirty percent of patients with lung cancer were estimated to result in the obstruction of their trachea and principal bronchi (4).

Interventional bronchoscopy enables patency to maintain of airway, palliating symptoms immediately in these patients (5). Bronchoscopy options for these MAO patients include electrocautery (6), stenting (7), laser resection (8), argon plasma coagulation (9,10), airway mechanical debridement and photodynamic therapy (11,12). Measures such as high-frequency electric or argon plasma coagulation and laser photoresection should be considered in intraluminal tumors (13,14). Stenosis caused by extrinsic compression of tumors or metastatic lymph nodes can be treated by airway stenting (15-17). However, although airway interventional treatments are effective in alleviating the clinical symptoms of patients with central airway stenosis (2,18), accompanying complications are common. In patients with stent implantation, granulation tissue hyperplasia, stent displacement, stent fracture, phlegm thrombus formation and other complications such as atelectasis and infection occur frequently (19-21). In addition, secondary to malignancies, the underlying diseases of these patients are usually critical. Therefore, their prognosis is often not satisfactory in clinical practice. More supporting evidence of the efficacy of treatments on MAO patients is needed to better understand their

prognosis. Moreover, exploring prognosis and potential prognostic risk factors among these populations can better procedure optimization and personalized clinical management. In this context, we first analyzed the short and intermediate efficacy of MAO patients undergoing interventional bronchoscopy. Then, the impacts of different interventional therapies and other clinical indicators on patients' prognosis were explored. By machine learning and statistical analysis, the risk-score and nomogram model were further constructed after repeated validations. Relevant data was also collected from another institute as an external dataset for verification. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/tlcr-21-301>).

Methods

Data collection and cohort development

We retrospectively identified a total of 240 patients who underwent interventional bronchoscopy at Shanghai Pulmonary Hospital between October 31, 2016, and July 31, 2019 and included 150 patients who had histologically-confirmed MAO (Table S1). Data screening excluded 52 (34.7%) with missing data and indicated 98 (65.3%) patients were available for analyzing the short and intermediate benefits of therapeutic bronchoscopy for MAO (Table S2). As for long-term prognosis evaluation, complete follow-up data of 112 patients were collected for survival analysis. After removing 8 patients with unspecific pathological types and 2 patients with histology of large cell neuroendocrine carcinoma and sarcomatoid carcinoma, 102 patients were available for model construction (Table 1, Figure 1).

Two experienced pathologists (ZLP, HLK) further evaluated and verified these primary diagnoses. Histologically-confirmed MAO patients over 18 years old who received bronchoscopy were included. Adenoid cystic carcinoma is classified as a type of non-small cell lung cancer (NSCLC), but quite different from NSCLC in several aspects (22). Adenoid cystic carcinoma mainly grows in tracheal lumen, with a relatively slower growth rate. It rarely develops metastasis to lymph node and other distant organs even in the advanced stages (22). Therefore, a TNM staging method was proposed by Bhattacharyya (23). In our study, we used Bhattacharyya staging criteria for adenoid cystic carcinoma (23) and the eighth edition of TNM classification for squamous cell carcinoma (SCC), adenocarcinoma (ADC), and small cell carcinoma (small cell lung cancer, SCLC) of lung cancer (24). No esophagus cancer patient was enrolled in our study. The main exclusion criteria were cases <18 years old, pathologically-confirmed benign airway stenosis, having not received treatment of interventional bronchoscopy, and with inadequate baseline clinical characteristics. The major basic clinical features included gender, age, smoking history, clinical stage, pathological category, operative site, airway stenosis classification, specific method of the interventional bronchoscopy, treatments including chemotherapy, radiotherapy, immunotherapy, and targeted therapy after interventional bronchoscopy, receiving interventional

bronchoscopy again due to restenosis, survival status, and overall survival (OS). OS was calculated from the specific date of interventional bronchoscopy to patients' death resulted from any reason. Short and intermediate benefits were defined radiologically as reopening patients' airway lumens to more than 50% of normal diameters. This study was conducted consistent with the provisions of Declaration of Helsinki (as revised in 2013). Approval from the ethics committee of Shanghai Pulmonary Hospital was obtained (18Q016NJ) and individual consent for this retrospective analysis was waived.

External data and validation cohort

Between January 6, 2016 and May 17, 2019, a total of 33 MAO patients undergoing bronchoscopy, with complete clinical information and the same clinical factors as our cohort for model development, were included as the validation cohort from the Second Affiliated Hospital of Zhejiang University, China. Patients in the validation cohorts were aged >18 years old and received therapies based on the protocol consistent with the development cohort. All of these patients had complete data for preoperative and postoperative computerized tomography (CT) scans. Short-period efficacy (<30 days) of bronchoscopy was verified. After follow-up, 24 (24/33, 72.7%) patients were available for survival analysis (Figure 1).

Table 1 Clinical characteristics of the cohort for survival study and model construction

Clinical characteristics	Survival analysis dataset (n=112)	Model construction dataset (n=102)
Age, median (range)	62 (26–89)	62 (26–89)
Sex, n (%)		
Male	92 (82.1)	85 (83.3)
Female	20 (17.9)	17 (16.7)
Smoking history, n (%)		
Current/former	51 (45.5)	46 (45.1)
Never	61 (54.5)	56 (54.9)
Clinical stage, n (%)		
Stage II	2 (1.8)	2 (2.0)
Stage III	76 (67.9)	70 (68.6)
Stage IV	34 (30.4)	30 (29.4)

Table 1 (continued)

Table 1 (continued)

Clinical characteristics	Survival analysis dataset (n=112)	Model construction dataset (n=102)
Histopathology, n (%)		
Squamous cell carcinoma	66 (58.9)	65 (63.7)
Adenocarcinoma	22 (19.6)	21 (20.6)
Small cell lung cancer	6 (5.4)	6 (5.9)
Adenoid cystic carcinoma of trachea	10 (8.9)	10 (9.8)
Large cell neuroendocrine carcinoma	1 (0.9)	0 (0.0)
Sarcomatoid carcinoma	1 (0.9)	0 (0.0)
Unspecific pathological types	8 (7.1)	0 (0.0)
Interventional surgery, n (%)		
Electrocoagulation alone	58 (51.8)	57 (55.9)
Stent alone	17 (15.2)	14 (13.7)
Laser alone	2 (1.8)	2 (2.0)
Electrosurgical snare	1 (0.9)	1 (1.0)
Combined therapy	34 (30.4)	28 (27.5)
Lesion site*, n (%)		
Trachea	35 (31.3)	32 (31.4)
Carina	14 (12.5)	12 (11.8)
Right principal bronchus	40 (35.7)	36 (35.3)
Right middle bronchus	14 (12.5)	11 (10.8)
Left principal bronchus	33 (29.5)	32 (31.4)
Lobar bronchus	11 (9.8)	11 (10.8)
Airway stenosis classification, n (%)		
External compression type	10 (8.9)	8 (7.8)
Intraluminal type	23 (20.5)	22 (21.6)
Mixed stenosis	79 (70.5)	72 (70.6)
Respiratory failure before bronchoscopy, n (%)		
Yes	2 (1.8)	2 (2.0)
No	110 (98.2)	100 (98.0)
Treatment after interventional bronchoscopy, n (%)		
Chemotherapy	59 (52.7)	55 (53.9)
Radiotherapy	45 (40.2)	38 (37.3)
Targeted therapy	4 (3.6)	4 (3.9)
Immunotherapy	7 (6.3)	6 (5.9)
Receiving interventional bronchoscopy again, n (%)		
Yes	7 (6.3)	7 (6.9)
No	105 (93.8)	95 (93.1)

The "*" indicates patients with more than one surgical site.

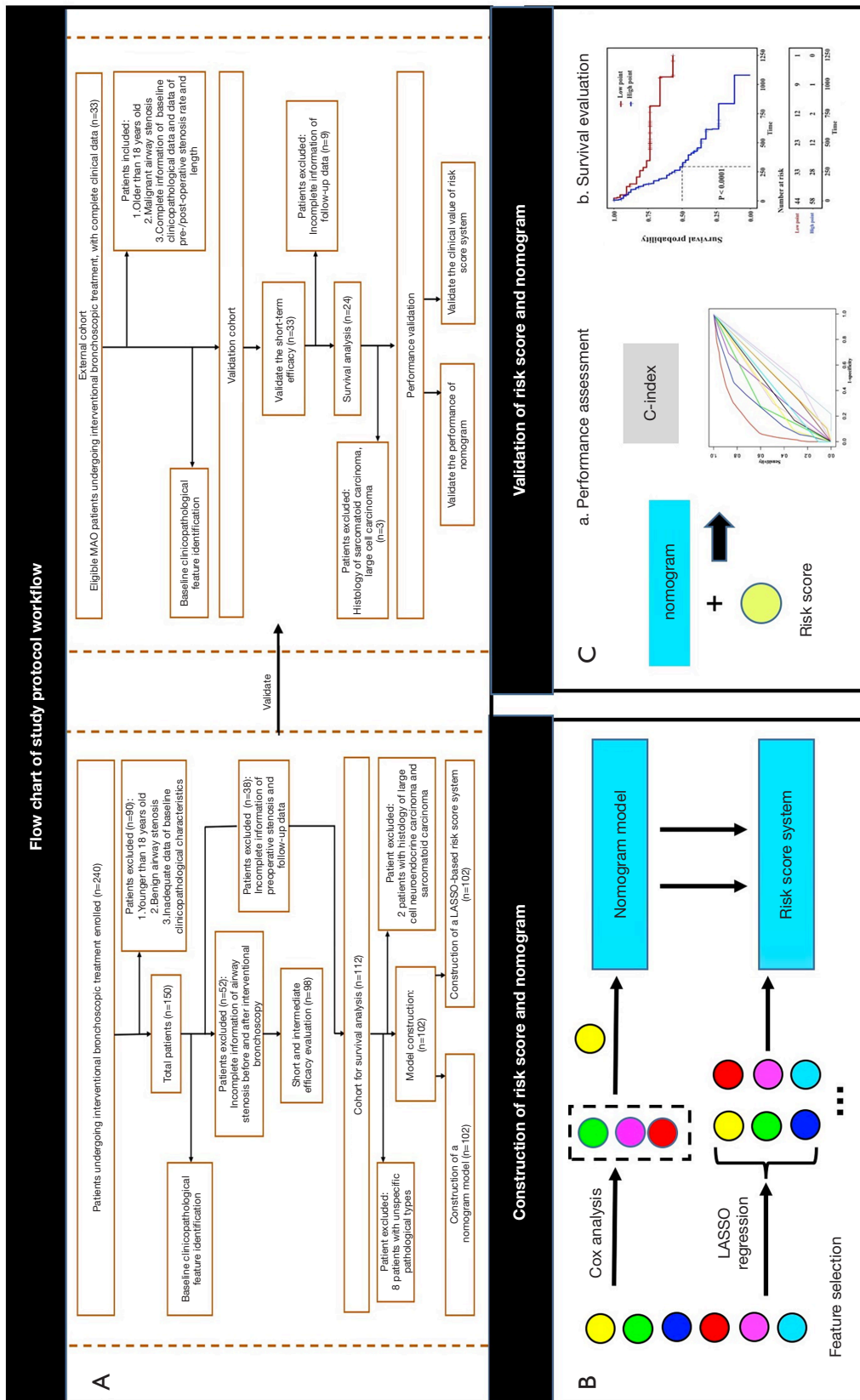


Figure 1 Study design workflow. (A) Flow chart of our study design. In this study, 240 patients were treated with bronchoscopy, in which 150 were histologically-confirmed MAO patients. 98 (65.3%) patients were available for analyzing short and intermediate benefits of therapeutic bronchoscopy for MAO. 112 patients with complement follow-up data were collected for survival analysis. The major experiments included: construction and verification of the risk score system and nomogram algorithm. (B) Establishment of the risk score and nomogram. (C) Validation of the risk score and nomogram model. LASSO, least absolute shrinkage and selection operator regression; MAO, malignant airway obstruction.

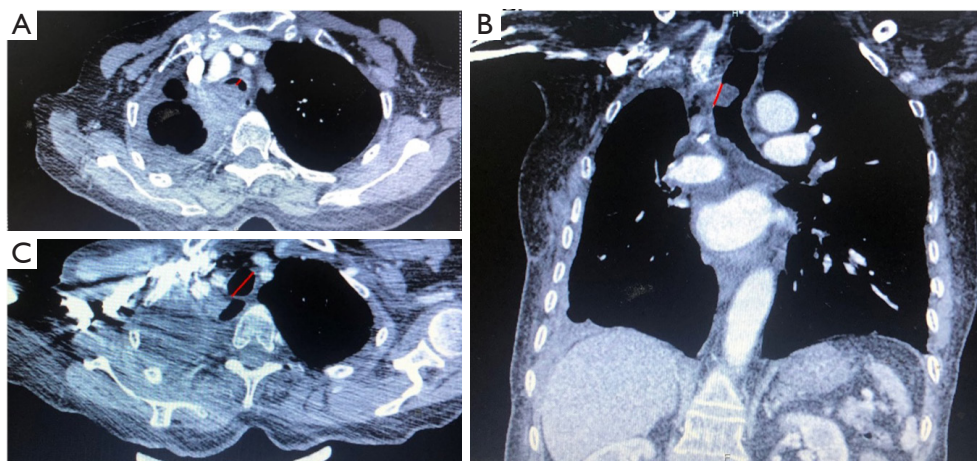


Figure 2 Measurement of the airway stenosis indexes. Lumen diameters were measured in mediastinal window of the dynamic enhanced chest computerized tomography (CT) scans. CT scans of (A) the minimum inner diameter of the stenosis, (B) the stenosis length of the narrow length of the airway, and (C) the inner diameter of the adjacent normal airway. CT, computerized tomography.

Therapeutic bronchoscopy for MAO in our study

Interventional therapies were performed by the experienced bronchoscopy specialists (YG, DMY, and LY), which included electrocoagulation (40 W), stenting, treatment of electrocoagulation plus stenting, treatment of electrocoagulation plus electrosurgical snare, treatment of electrocoagulation, electrosurgical snare, plus stenting, and laser (20 W) in this study. High-frequency electrosurgical equipment (Tübingen, Germany), metal stent (Nedick, Massachusetts, USA), and semiconductor laser system (Montgomeryville, Pennsylvania, USA) were used. The selection criteria of the interventional bronchoscopy were best determined by stenosis types (25): ablation such as electrocoagulation, electrosurgical snare, and laser were utilized for simple intraluminal malignancies; stents could be placed for simple external stenosis; treatment of ablation plus stent implantation was used for mixed stenosis (25). Specifically, we mainly used laser for tumors causing central airway stenosis and patients with severe shortness of breath; and used electrosurgical snare for tumors with narrow bases. The use of electrocoagulation is relatively wide; however, it was not appropriate for tumors with extremely hard texture, for which laser was the suitable ones. The use of combined therapies was individualized, considering the characteristics of the tumor, such as morphology, compression, and texture, to better treat patients and efficiently relieve symptoms. The specific methods should be determined according to the actual situation of patients. General anesthesia was applied for interventional bronchoscopy and flexible

bronchoscopy was used for the procedure.

Imaging analysis

Lumen diameters were measured in the mediastinal window of the dynamic enhanced chest CT scans. Measurement of the airway diameter included two parts. First, we measured the minimum lumen diameter of stenosis. We then measured the nearest proximal portion of normal diameter, paralleling to the minimum lumen diameter of stenosis. If the top of the trachea was invaded by tumor, we measured the nearest distal portion of normal diameter. When measuring the stenosis length, we manually marked the origin and end of the stenosis in the coronal position of the CT scans (Figure 2). The stenosis rate was calculated as $(1 - \text{the minimum lumen diameter}/\text{the nearest distal or proximal portion of normal diameter}) \times 100\%$ (26).

$$\text{Stenosis rate} = (1 - d1/d2) \times 100\% \quad [1]$$

The d1 was defined as the minimum lumen diameter of the stenosis; d2 was defined as the nearest distal or proximal portion of normal diameter.

Determination of imaging cutoff for stenosis rate and length

We defined the high result as more than 88.46% for preoperative rate or more than 3.91 centimeters for stenosis length. Best cutoff values were determined using the R survminer package.

Nomogram construction and internal verifications

We randomly divided the whole dataset with 102 patients into training and testing cohorts by R programming (7:3). Parameters selected from Cox regression and clinical stage were chosen as factors. Nomogram model was constructed by using “rms” R package. The performance of this nomogram was measured using the concordance index (C-index) and time-dependent receiver operating characteristic (ROC) curve analyses. Further, Kaplan-Meier survival analyses were performed to evaluate the clinical value of this nomogram model (Figure 1).

Construction of the risk-score system

Unlike stepwise regression, method of least absolute shrinkage and selection operator (LASSO) regression is able to select independent factors by processing all variables (27,28), which increases model stability dramatically. Clinical factors that were most relevant to survival of MAO patients were screened by using package “glmnet” in R. We also used “cv.glmnet” function for cross validation, avoiding overfitting, and constructed regression models incorporating selected parameters using Cox regression method. To develop a risk score system for MAO patients, we incorporated the factors selected from model with the optimal performance for Cox multivariate analysis. Risk score for these MAO patients was calculated: Risk score = $(0.421 \times \text{age}) - (0.039 \times \text{sex}) + (0.645 \times \text{smoking status}) + (0.076 \times \text{clinical stage}) - (0.413 \times \text{receiving interventional bronchoscopy again due to restenosis}) - (0.213 \times \text{intraluminal subtype}) + (0.427 \times \text{external compression subtype}) - (1.464 \times \text{histology}) + (0.476 \times \text{stenosis rate}) + (0.817 \times \text{stenosis length}) - (0.504 \times \text{radiotherapy after interventional bronchoscopy}) + (0.143 \times \text{immunotherapy after interventional bronchoscopy}) - (1.884 \times \text{targeted therapy after interventional bronchoscopy})$. Furthermore, we proved its risk-discrimination capability among MAO patients and compared it with the single variables and nomogram model (Figure 1).

External validation of the nomogram model

When using an external cohort for nomogram validation, we calculated the total points for each participant based on the established model. Then, we set the factor by the total points and conducted Kaplan-Meier survival analysis. In addition, C-index as well as ROC curves were derived according to the analysis in this external cohort (29).

Statistical analysis

Variables with statistical significance ($P < 0.05$) in the univariate analysis were chosen entering into the multivariate model. Considering multiple clinical parameters, logistic regression analysis was conducted for predicting short and intermediate benefits. We also used Kaplan-Meier analyses and Cox regression for comparing prognosis conditions among diverse populations. For multivariate Cox regression, factors with P value < 0.1 in the univariate Cox analysis and clinical stage were included for analysis. OS was determined as the end point. All models used in our study met the prerequisites. We used the area under the receiver-operating characteristic curve (AUC) to evaluate the discriminative capability of the models. Data analysis and visualization were performed using R version 3.6.1 (R Foundation for Statistical Computing), GraphPad Prism version 7 for Mac OS X (GraphPad Software, San Diego, California), Excel (Excel for Mac 2016, Microsoft, Redmond, Washington), and SPSS statistical software version 26.0 (IBM Corp., Armonk, New York). A two-tailed $P < 0.05$ was defined as statistical significance.

Results

Clinicopathological characteristics

In our study, patients are predominantly male (81.3%) and the median age was 62.0 years (Table S1). 147 (98.0%) patients had clinical advanced-stage (III–IV) malignant disease and most tumors were SCC and ADC (73.3%). For the dataset to study survival, most were males, with a mean age of 61.7 ± 9.9 years. 98.2% patients were at advanced stages (stage III–IV) and SCC was the most common histologic subtype (Table 1). Minimal bleeding was observed during the procedures among these patients. 6.3% patients (7/112) had restenosis and all of these patients with restenosis received interventional bronchoscopy again (Table 1).

Short and intermediate benefits

To investigate the short (within 30 days) and intermediate efficacy (more than 30 days) among MAO patients undergoing interventional bronchoscopy, we identified and compared the stenosis rate of each patient before and after the therapy. In all 98 patients, we observed a significant decline of airway stenosis after bronchoscopy from $71.7\% \pm 2.1\%$ to $36.6\% \pm 2.7\%$ ($P < 0.001$) (Figure 3A,B,C,D,E). Among them,

67 (67/98, 68.4%) showed short or intermediate benefits (the postoperative lumen reopened more than 50% of the normal), which indicated that bronchoscopic therapy could dilate patient's airway effectively. Considering the diversely clinical classifications of bronchoscopic therapies, we further surveyed the therapeutic efficacy of each interventional program. It is worth noting that stenosis rate before receiving treatment of electrocoagulation (*vs.* after electrocoagulation therapy 70.3%±3.3% *vs.* 40.7%±3.8%, $P<0.001$), stenosis rate before receiving treatment of stenting (*vs.* after stenting therapy 68.9%±4.3% *vs.* 25.6%±4.7%, $P<0.001$), stenosis rate before receiving treatment of electrocoagulation in combination with electrosurgical snare (*vs.* after combined therapy 79.1%±3.5% *vs.* 44.5%±7.4%, $P<0.001$), stenosis rate before receiving treatment of electrocoagulation in combination with stenting (*vs.* after combined therapy 79.2%±5.3% *vs.* 34.3%±9.0%, $P<0.001$) marked declined, echoing the conception that interventional bronchoscopic therapy was very useful to relieve symptoms (*Figure 3B,C,D,E*). Among different operations, electrocoagulation in combination with airway stent implantation showed the maximal decline of stenosis rate (44.82% before and after therapy) (*Figure 3E*). Thus, interventional bronchoscopy played an important role in improving the short- and intermediate conditions of patients with MAO. In addition, we also identified the roles of clinical characteristics in predicting short and intermediate benefits of MAO. However, we failed to find determinants of the short and intermediate outcomes ($P>0.05$; *Table S3*).

For short-term efficacy, in all 38 MAO patients, similar results were showed (*Figure S1*). Intermediate efficacy was also observed with significant stenosis improvement in 60 MAO patients (*Figure S2*). With continuous follow-up (from the first-time operation to death or deadline for follow-up), lumen restenosis was observed in 6 of these 98 (6/98, 6.1%) MAO patients (*Figure S3*).

Prognosis of MAO patients after interventional bronchoscopy

We obtained 112 samples with complete survival data (*Figure 3F*), with a median survival time of 614.000 days (95% CI: 269.876–958.124; *Figure 3G*). In all 66 MAO patients less than 65 years old, 25 (37.9%) reached the end event for OS (median 1,065.000 days, 95% CI: undefined). For 46 patients more than 65 years old, the median OS was 288.000 days (95% CI: 121.514–454.486), among them 16 (16/46, 34.8%) had survived. Kaplan–Meier analysis showed that the basic characteristics including age

($P=0.004$), smoking status ($P=0.005$), preoperative stenosis rate ($P=0.006$) were significantly associated with MAO OS (*Table S4*). Meanwhile, stenosis site ($P=0.056$) and airway stenosis classification ($P=0.051$) were analyzed as marginally significant factors for MAO OS. There was no statistical difference in survival observed in clinical stage II–III and IV ($P=0.465$). 102 patients were available for studying the impacts of histology on patients' prognosis. As *Figure 3H* showed, adenoid cystic carcinoma had better prognosis than SCC ($P=0.002$), ADC ($P=0.008$), and SCLC ($P=0.006$).

Then, we evaluated the prognosis of MAO patients undergoing different interventional methods (*Figure 3I,J,K,L,M*). Among all therapeutic bronchoscopies except electrosurgical snare ($n=1$), patients receiving treatment of electrocoagulation plus electrosurgical snare showed the longest survival, followed by receiving electrocoagulation alone, receiving stenting alone, and combining electrocoagulation and stenting (*Figure 3M*, $P=0.022$). Four patients received laser treatment and have maintained good condition after surgery, with a period of 494, 448, 474, and 663 days respectively since the operation. The OS of two patients receiving the combined therapy of electrocoagulation, electrosurgical snare and stenting was lower than the median survival (147 and 55 days respectively).

COX regression for OS in MAO

To excavate the potential factors influencing the survival, we used patients' baseline clinicopathological features for regression analysis (*Table 2*). A total of 102 MAO patients with known histological diagnosis were enrolled for the study. Univariate analysis revealed age <65 years ($P=0.007$), nonsmoking status ($P=0.004$), adenoid cystic carcinoma ($P=0.016$), and low stenosis rate ($P=0.007$), as being associated with better OS significantly. Intriguingly, multivariate analysis identified nonsmoking status, adenoid cystic carcinoma, and low preoperative stenosis length as independent predictive factors for better OS of MAO patients [*vs.* smokers, HR=0.425, 95% CI: 0.228–0.794, $P=0.007$; *vs.* non-adenoid cystic carcinoma (SCC, ADC, and SCLC), HR=0.100, 95% CI: 0.011–0.898, $P=0.040$; high preoperative stenosis length, HR=0.409, 95% CI: 0.207–0.811, $P=0.011$].

Nomogram model for prognostic prediction

Given the significant results of Cox regression and the

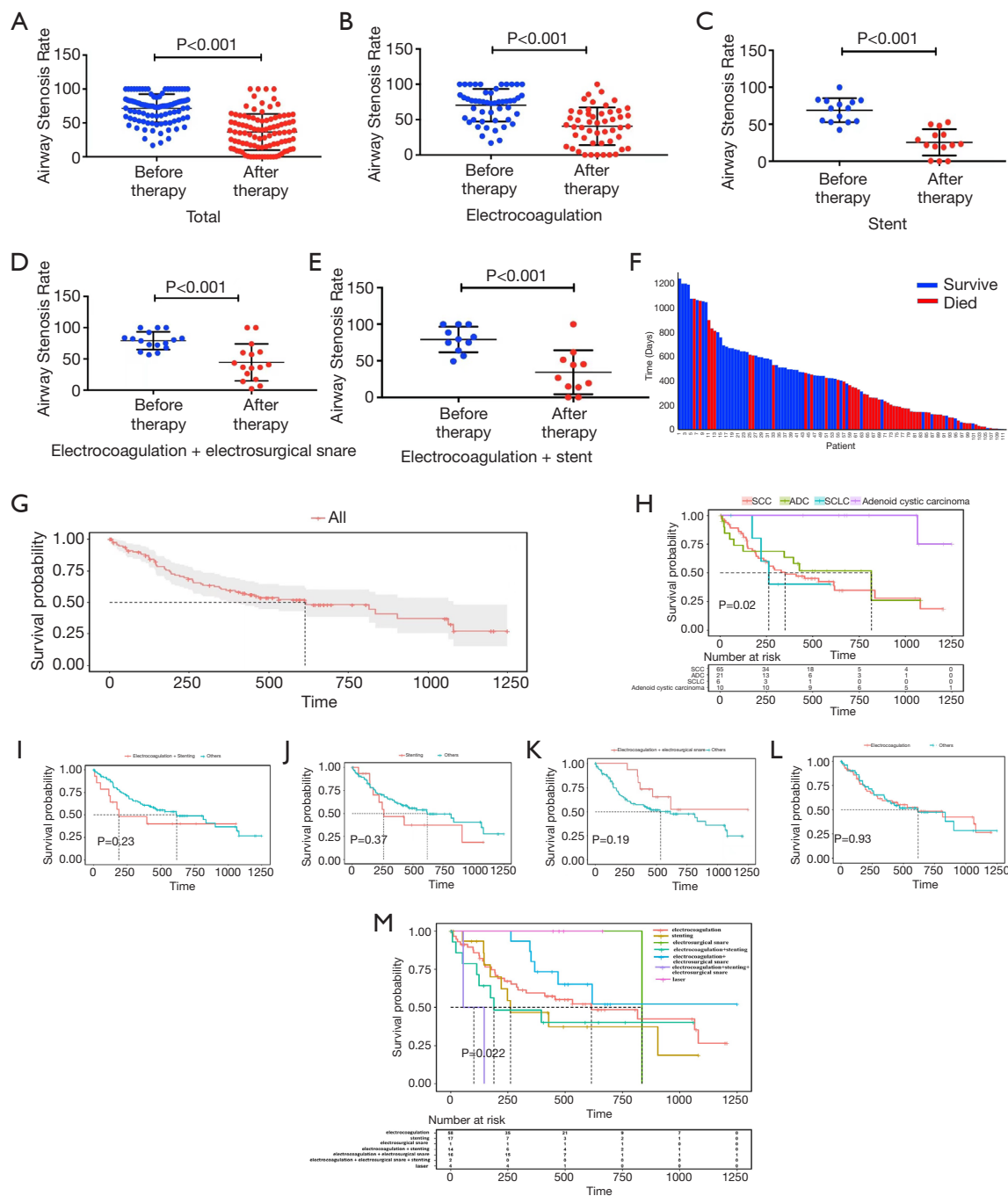


Figure 3 Airway stenosis rate before and after treatment and survival of MAO patients undergoing interventional bronchoscopy. Stenosis rate changes with interventional bronchoscopic therapies including (A) all treatments involved (N=98), (B) electrocoagulation alone (N=50), (C) stenting alone (N=14), (D) combining therapy of electrocoagulation and electrosurgical snare (N=16), (E) combining therapy of electrocoagulation and stenting (N=11), (F) Survival status and survival period. 112 patients with complete survival data were enrolled for survival study. (G) The Kaplan-Meier survival curves of 112 patients. (H) Kaplan-Meier survival analysis of MAO patients based on histological subtypes (n=102). (I,J,K,L) The Kaplan-Meier survival curves comparing prognosis of MAO patients receiving electrocoagulation plus stenting, stenting implantation, electrocoagulation plus electrosurgical snare, or electrocoagulation, with others respectively. (M) The Kaplan-Meier survival analyses of distinct therapeutic bronchoscopic methods. MAO, malignant airway obstruction; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small-cell lung cancer.

Table 2 Univariate and multivariate analysis of MAO patients undergoing interventional bronchoscopy

Factor	No. of patients		Univariate analysis			Multivariate analysis		
	N, %	N, %	HR (log rank)	95% CI	P value	HR (log rank)	95% CI	P value
Sex (female vs. male)	17, 16.7	85, 83.3	0.541	0.230–1.273	0.159			
Age (<65 vs. ≥65)	61, 59.8	41, 40.2	0.468	0.271–0.809	0.007	0.580	0.319–1.055	0.074
Smoking (nonsmoker vs. smoker)	56, 54.9	46, 45.1	0.435	0.246–0.770	0.004	0.425	0.228–0.794	0.007
Stage (II-III vs. IV)	72, 70.6	30, 29.4	1.305	0.704–2.421	0.398	0.693	0.352–1.365	0.693
Lesion and surgical site (Trachea and carina vs. bronchus)	41, 40.2	61, 59.8	0.638	0.355–1.146	0.133			
Stenosis subtypes					0.080			0.232
Stenosis subtypes (intraluminal type vs. mixed type)	22, 21.6	72, 70.6	0.457	0.204–1.024	0.057	0.771	0.320–1.861	0.563
Stenosis subtypes (external compression vs. mixed type)	8, 7.8	72, 70.6	1.581	0.617–4.051	0.340	2.152	0.785–5.904	0.137
*Histology (non-adenoid cystic carcinoma vs. adenoid cystic carcinoma)	92, 90.2	10, 9.8	11.592	1.583–84.889	0.016	9.994	1.113–89.698	0.040
Stenosis rate (low vs. high)	81, 79.4	21, 20.6	0.435	0.237–0.798	0.007	0.639	0.325–1.254	0.193
Stenosis length (low vs. high)	77, 75.5	25, 24.5	0.598	0.326–1.097	0.097	0.409	0.207–0.811	0.011
Chemotherapy after interventional bronchoscopy (no vs. yes)	47, 46.1	55, 53.9	1.043	0.600–1.813	0.881			
Radiotherapy after interventional bronchoscopy (no vs. yes)	64, 62.7	38, 37.3	1.558	0.860–2.822	0.143			
Targeted therapy after interventional bronchoscopy (no vs. yes)	98, 96.1	4, 3.9	21.463	0.031–14997.714	0.359			
Immunotherapy after interventional bronchoscopy (no vs. yes)	96, 94.1	6, 5.9	0.603	0.216–1.680	0.333			
Receiving interventional bronchoscopy again (no vs. yes)	95, 93.1	7, 6.9	1.643	0.506–5.334	0.409			

HR, hazard ratio; MAO, malignant airway obstruction; 95% CI, 95% confidence interval. *, non-adenoid cystic carcinoma: squamous cell carcinoma, adenocarcinoma, small cell lung cancer.

important value of clinical stage, we incorporated smoking status, preoperative stenosis length, histologic subtype, and clinical stage, to establish the quantitative means for survival prediction of MAO (Figure 4A). Then, we used C-index for evaluating its predictive value, and the nomogram system performed well with the C-index of 0.668, 0.695, and 0.669 in the training, testing, and whole MAO cohorts, respectively. Further, 1-, 2-, and 3-year time-dependent ROC curves also indicated excellently predictive ability (AUC 0.651, 0.783, and 0.739 for the training cohort respectively; for the testing cohort, all of the AUC values were 0.738; Figure 4B,C).

Moreover, based on the median value of the total points calculated from this nomogram, we further divided these 102 MAO patients into higher score and lower score groups. Patients with lower score exhibited the higher survival rate compared with those with higher score (for the entire cohort, third quantile of OS: low score *vs.* high score, 346.000 days, 95% CI: 0.000–902.050 *vs.* 144.000 days, 95% CI: 94.185–193.815; $P < 0.001$; for training cohort, third quantile of OS, low score *vs.* high score, 816.000 days, 95% CI: 0.000–1,811.619 *vs.* 150.000 days, 95% CI: 35.166–264.834; $P = 0.001$; for testing cohort, third quantile of OS: low score *vs.* high score, 261.000 days, 95% CI: 19.920–502.080 *vs.* 126.000 days, 95% CI: 74.419–177.581; $P = 0.050$; Figure 4D,E,F).

Construction of risk-score system based on LASSO regression

Considering widespread relationships of clinical parameters with MAO prognosis, we proposed to perform LASSO regression for feature selection and construct a fusion biomarker for prognostic evaluation of MAO. The optimal model selected by LASSO was constructed incorporating 13 indicators including age, sex, smoking status, clinical stage, intraluminal subtype, external compression subtype, histology, preoperative stenosis rate, preoperative stenosis length, radiotherapy after interventional bronchoscopy, immunotherapy after interventional bronchoscopy, targeted therapy after interventional bronchoscopy, as well as receiving interventional bronchoscopy again (Figure 5A,B). Thus, these 13 indicators were chosen for risk-score construction. This risk score achieved excellent performance, with AUC values of 0.785, 0.855, and 0.880 for 1, 2, and 3-year time-dependent ROC curves. Compared with single indicator, this risk score demonstrated better performance. Time-dependent ROC analyses indicated the risk-score with the maximum AUC value of 0.855,

while 0.662, 0.598, 0.574, 0.476, 0.466, 0.596, 0.392, 0.615, 0.573, 0.403, 0.555, and 0.459 for single parameters smoking status, age, gender, clinical stage, receiving interventional bronchoscopy again, stenosis classification, histology, preoperative stenosis rate, preoperative stenosis length, radiotherapy or immunotherapy or targeted therapy after interventional bronchoscopy when selecting cutoff value as two years (Figure 5C). Considering the good performance of nomogram, we also compared this risk score system with nomogram. Time-dependent ROC curve showed that the AUC values were 0.855 and 0.739 respectively (Figure 5C), which indicated that this risk score system performed better than the nomogram model to predict prognosis of MAO patients. Using the median value of risk score for risk classification, survival curves showed that high risk-score group had poorer prognosis than low risk-score group (third quantile of OS: 126.000 days, 95% CI: 73.588–178.412 *vs.* 532.000 days, 95% CI: 0.000–1,110.372; $P < 0.001$; Figure 5D). Univariate Cox regression also analyzed the significant difference between this score and MAO survival (low score *vs.* high score HR=0.181, 95% CI: 0.093–0.351; $P < 0.001$).

Validation by external data

Clinical characteristics of external MAO patients were summarized (Table S5). Complete preoperative and postoperative stenosis data of MAO patients were available for thirty-three samples. For short-term efficacy, 23 patients (23/33, 69.7%) showed airway reopened more than 50%. Significant differences before and after interventional bronchoscopy were observed in the entire MAO validation cohort ($P < 0.001$), patients with electrocoagulation in combination with stenting ($P < 0.001$), and patients with single electrocoagulation therapy ($P = 0.001$; Figure 6A,B,C). Among the external dataset, a total of twenty-four patients were available for survival analysis. In the validation cohort for survival analysis, 95.8% (23/24) patients reached end points, with a median OS of 122.000 days (95% CI: 15.178–228.822). Survival analysis of MAO patients in the validation participants was summarized in Table S6. We also verified the prognostic value of the risk-score in this external verification cohort. When applying the same methods to define cutoff values of preoperative stenosis rate and length, we found that the 1-, 2-, 3-year time-dependent ROC analyses also validated good performance of this LASSO-based model, with AUC values of 0.800, 0.739, and 0.739 respectively (Figure 6D). In addition, using the median

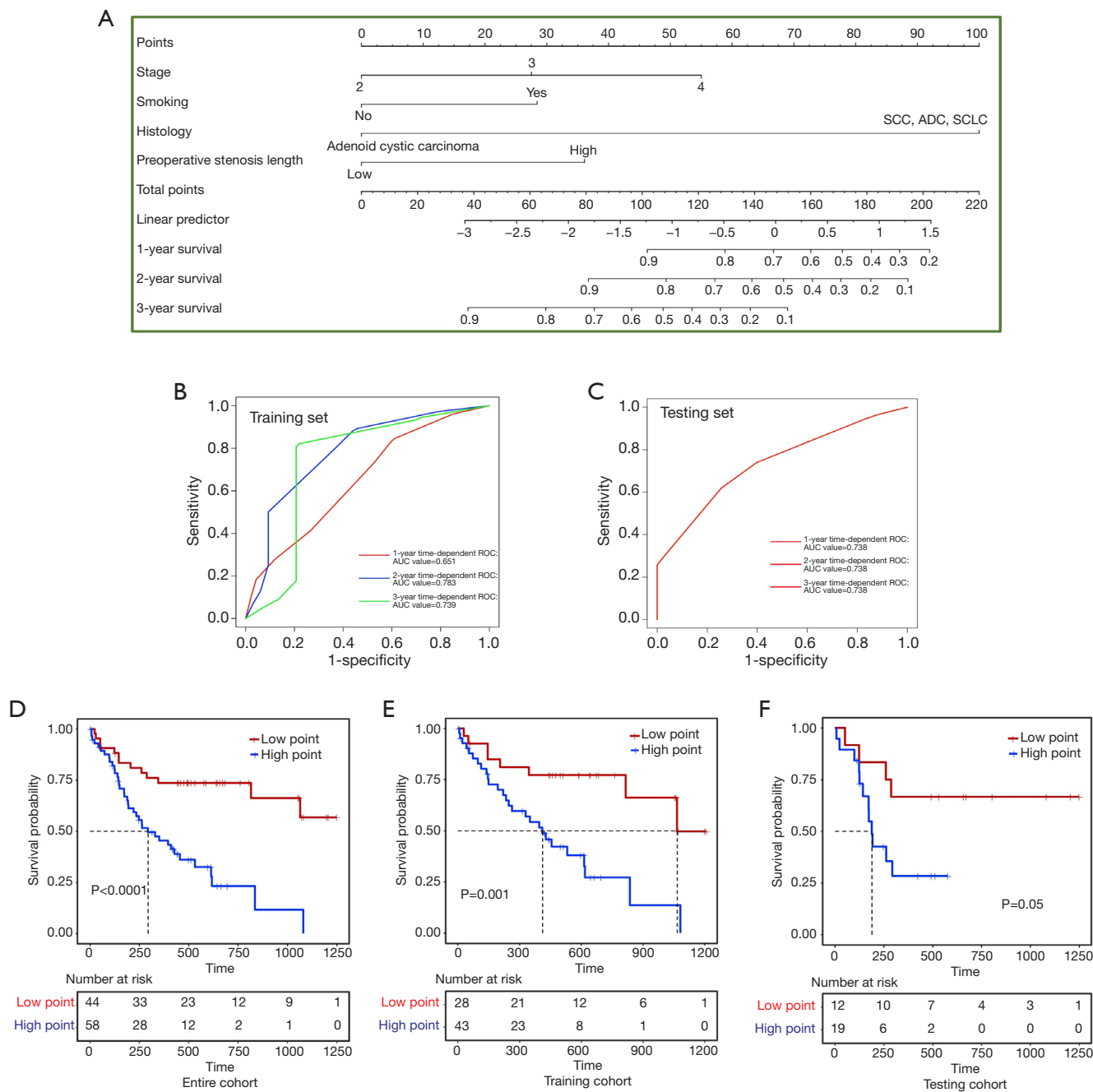


Figure 4 Construction and clinical value evaluation of the prognosis nomogram model for MAO. (A) The nomogram model incorporated preoperative stenosis length, smoking status, clinical stage, and histology. (B,C) 1-, 2-, and 3-year time-dependent ROC curves in the training (N=71) and testing cohorts (N=31). (D,E,F) Survival analyses of patients in different total points of the nomogram model in the training, test, and whole MAO cohorts respectively. All three cohorts obtained excellent risk-grade division with significant differences. MAO, malignant airway obstruction; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small-cell lung cancer.

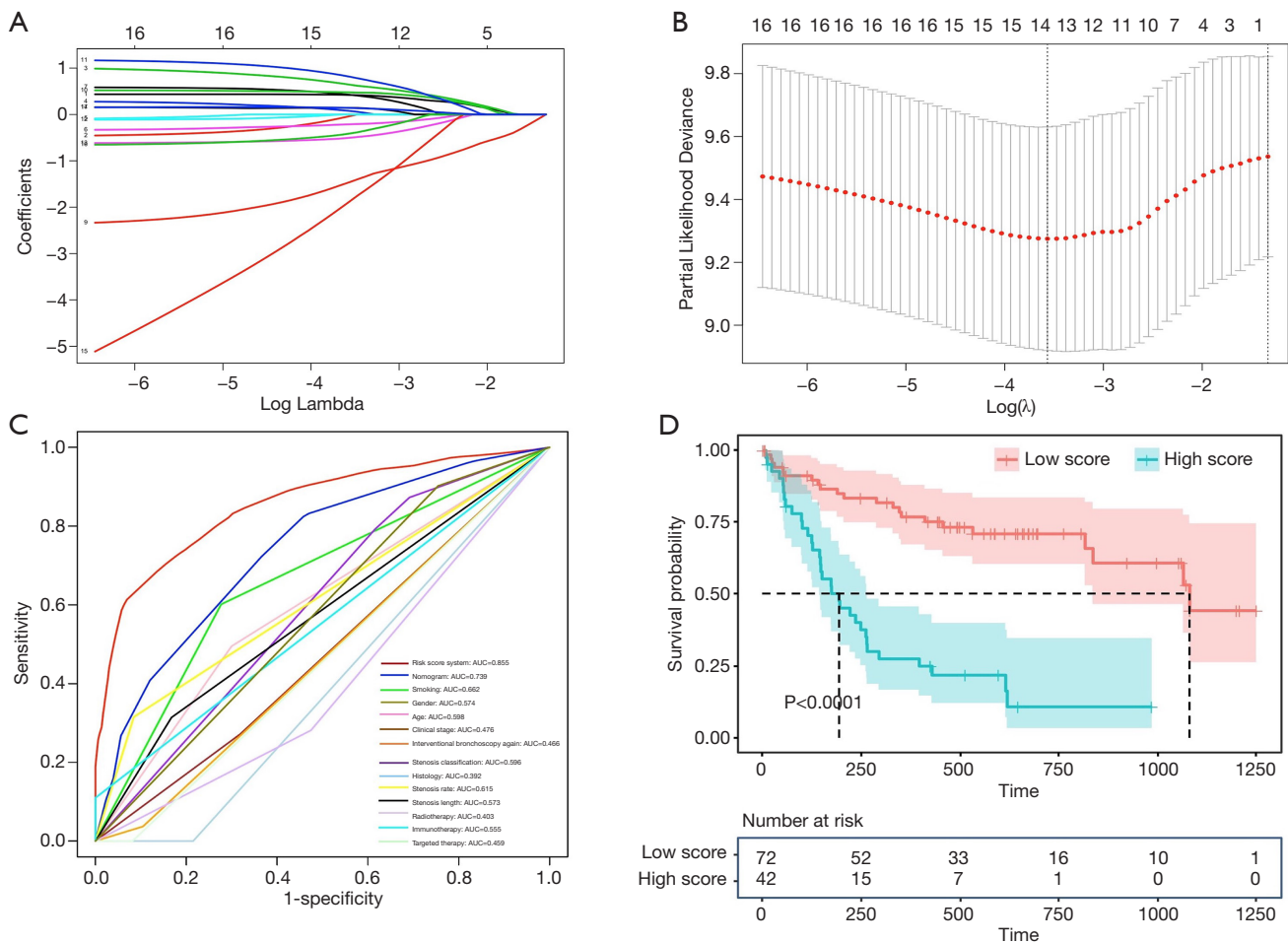


Figure 5 Risk score system and feature importance selection. (A,B) Method of LASSO for feature selection. The results by LASSO selected 13 variates (age, sex, smoking status, clinical stage, intraluminal subtype, external compression subtype, histology, preoperative stenosis rate, preoperative stenosis length, radiotherapy after interventional bronchoscopy, immunotherapy after interventional bronchoscopy, targeted therapy after interventional bronchoscopy, and receiving interventional bronchoscopy again due to restenosis), as predictive factors in all 102 MAO patients to construct the optimal model. (C) Time-dependent ROC analyses for performance evaluation of this predictive risk-score, nomogram, and other single biomarkers. The curves indicated the risk-score with the maximum AUC value of 0.855, compared with other biomarkers. (D) Survival analysis between high risk-score group and low risk-score group. AUC, area under the receiver-operating characteristic curve; ROC, receiver operating characteristic; LASSO, least absolute shrinkage and selection operator regression; MAO, malignant airway obstruction.

value of risk score for classification, we also found that MAO patients with low risk-score had higher OS (*vs.* high risk-score group 160.000 days, 95% CI: 0.000–466.804 *vs.* 63.000 days, 95% CI: 26.316–99.684; $P=0.015$; *Figure 6E*). Moreover, we also verified the performance and clinical value of this nomogram model (*Figure 6F,G*). Consistent with our developing cohort, this nomogram model showed relatively poorer performance than LASSO-based risk system, with a C-index of 0.619 as well as AUC values of 1-,

2-, 3-year time-dependent ROC of 0.720, 0.574, and 0.574, respectively. Patients with low nomogram points showed longer OS compared with those with high points (low *vs.* high, 160.000 days, 95% CI: 0.000–434.414 *vs.* 65.000 days, 95% CI: 0.000–136.634; $P=0.517$).

Discussion

In this study, we first investigated the therapeutic benefits

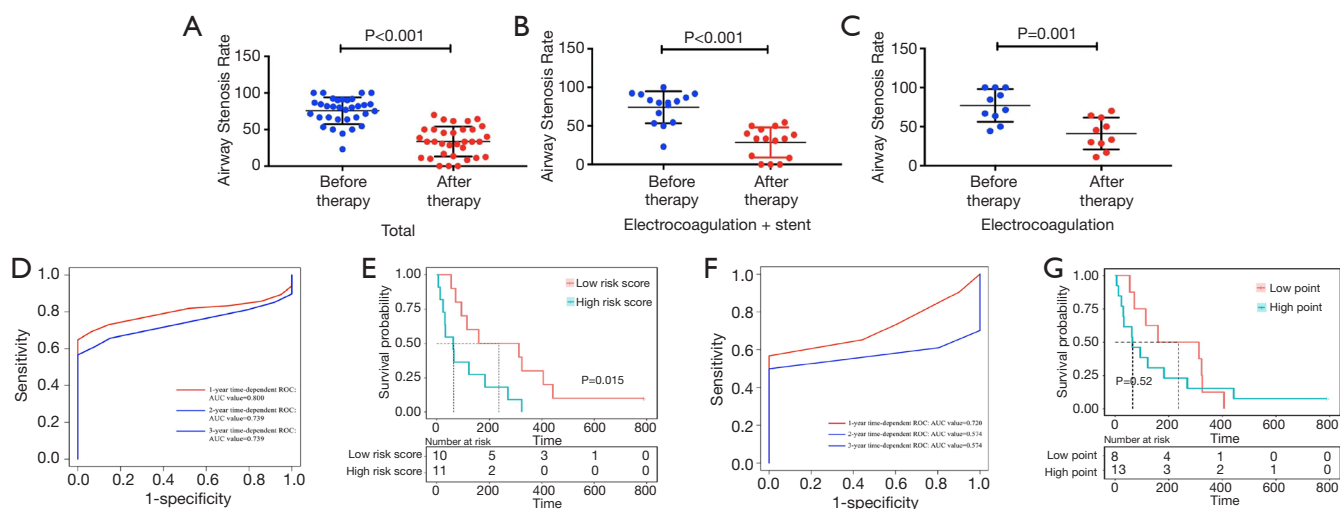


Figure 6 Validation of the risk score and nomogram model on the external data. (A,B,C) Significant differences before and after interventional bronchoscopy were observed in the entire MAO validation cohort ($P < 0.001$), patients with electrocoagulation in combination with stenting ($P < 0.001$), and patients with single electrocoagulation therapy ($P = 0.001$). (D) Time-dependent ROC for the LASSO-based risk score system. (E) Survival analysis of the risk-score in external dataset. (F) Time-dependent ROC for nomogram. (G) Survival analysis based on nomogram in external dataset. AUC, area under the receiver-operating characteristic curve; LASSO, least absolute shrinkage and selection operator regression; MAO, malignant airway obstruction; ROC, receiver operating characteristic.

of MAO patients undergoing interventional bronchoscopy and explored patients' prognosis of distinct methods of therapeutic bronchoscopy and other clinical characteristics. Then, univariate and multivariate Cox analyses were conducted and a nomogram predictive model based on histology, clinical stage, smoking status, and preoperative stenosis length was constructed for prognosis prediction of MAO. In addition, considering the impacts of different clinical factors on MAO prognosis, we then conducted LASSO algorithm, and established a well-performed risk score system incorporating 13 indicators including age, sex, smoking status, clinical stage, intraluminal subtype, external compression subtype, histology, preoperative stenosis rate, preoperative stenosis length, radiotherapy after interventional bronchoscopy, immunotherapy after interventional bronchoscopy, targeted therapy after interventional bronchoscopy, and receiving interventional bronchoscopy again due to restenosis. Interestingly, this risk score obtained a better AUC value than the above nomogram model and single indicators. We also verified the stenosis characteristics before and after bronchoscopy, as well as the clinical values of the nomogram model and risk score system in an external dataset, which further proved the good performance of LASSO-based risk score system. More prospective trials should be carried out for

verification.

As the results shown in our study, interventional therapy expanded airway successfully, which was similar to previous research results (2,30,31). Some previous studies also illustrated improvement in dyspnea and life quality after bronchoscopy (5,32-34). Airway restenosis was observed in 9 patients among all 150 MAO patients enrolled. The time from the first interventional bronchoscopy to receiving interventional bronchoscopy again due to restenosis in these patients ranged from 16 to 709 days. This restenosis could relate to tumor ingrowth or excessive mucus retention and granulation tissue (32,35-37). The restenosis of seven of the nine patients was caused by tumor ingrowth and two was caused by granulation tissue. Interventional pulmonology procedures were re-performed for all of these patients with restenosis. No severe complications were encountered.

Patients chosen for interventional bronchoscopy were mainly at advanced stages in our study. They suffered from airway stenosis in different degrees and some of them experienced symptoms such as chest tightness and shortness of breath. The main purpose of interventional bronchoscopy for these advanced patients was to remove blockage of airway, relieve symptoms, and prolong life to some extent. A total of 3 patients at stage II received interventional bronchoscopy in all 150 patients. Patient 1 had a severe

reduction of pulmonary ventilation, with the forced expired volume in one second as a percentage of expected value (FEV1% Pred) of 37.2%, combined with pulmonary bullae. For patient 2 and 3, during bronchoscopy, new organisms in the left lower lobar and right lower lobar bronchi were found respectively, which greatly clogged the tube cavity. Therefore, interventional bronchoscopy was recommended. The treatment of interventional bronchoscopy could help to keep the airway patency, assess the extent of tumor invasion, and provide guidance for resection range of surgery to some extent. The basic purpose of intervention for patients at early and advanced stages was to remove blockages and ensure airway patency. The median survival time was 614 days in this study, which was comparatively longer than the results of other published reports (2,15,38). Armin Ernst and colleagues showed a 30-day mortality of 7.8% in MAO patients after bronchoscopy, with common complications occurring, associated with intervention urgency and health status (39). Many studies also indicated that timely therapeutic bronchoscopy could improve patients' life quality and survival (34,40,41). We also evaluated patients' survival after distinct interventional bronchoscopies and found different clinical outcomes among them. They suffered from different degrees of stenosis by the tumor. Thus, it is important to explore the potential factors that might affect patients' survival.

In our study, we found that age <65 years old, non-smoking status, adenoid cystic carcinoma, and low preoperative stenosis rate, were significantly associated with longer OS in MAO patients ($P < 0.05$). After multivariate Cox regression incorporating more factors, the independently prognostic values of smoking status, histology, and preoperative stenosis length were revealed. Compared with endobronchial and mixed tumor types, patients with extrinsic tumors showed shorter OS; lesions in trachea and carina tended to have better clinical outcomes than bronchus lesions, although only marginally significant difference was revealed. Patients experienced respiratory failure before interventional bronchoscopy showed shorter OS compared with those with no respiratory failure. After bronchoscopy and intensive treatment, one patient survived for 396 days, and the other was still alive and having already survived for 513 days. However, only two patients with respiratory failure were included. For a better understanding of the prognosis of MAO patients with respiratory failure before bronchoscopy, a larger prospective study is needed. No MAO patient caused by esophageal cancer was enrolled for study, and more studies were

needed to explore the prognosis of MAO patients caused by tumors such as esophageal cancer. Previous study also suggested functional status, cardiac disease, dyspnea level, time from disease diagnosis to interventional bronchoscopy, bronchoscopic dilation and chemotherapy were correlated with MAO patients' prognosis (18). Thus, many factors should be considered when evaluating prognosis of MAO patients after interventional bronchoscopy.

Nomogram is increasingly developed as a promising method for predicting patients' prognosis, and several models could perform better than the traditional clinical systems (29,42,43). Thus, based on survival analysis, we first constructed a nomogram incorporating histology, clinical stage, smoking status, and preoperative stenosis length for prediction. In addition, considering multiple parameters could influence patients' survival, we further conducted LASSO regression and established a risk-score system with good performance to predict prognosis. Both predictive systems showed patients with low score exhibited higher survival rate as potential biomarkers. Thus, we then conducted time-dependent ROC curve analysis, given the well-performance of both models, to compare their performance. The risk-score system was proved better performed. Also, when compared with single biomarkers, this risk-score system exhibited the best performance. The AUC values were 0.855 and 0.476 for risk score system and staging, which indicated that this risk score might represent a promising method for prognosis evaluation when compared with the conventional stage system among these patients. It could predict patients' long-term prognosis receiving bronchoscopy better than the current stage system. Unlike single biomarkers, the risk score system combined both traditional staging system and other clinical parameters to construct a fusion biomarker, which is of great importance for the individualization of prognostic evaluation of MAO patients with interventional therapy.

To further understand patients' survival characteristics and evaluate clinical values of two predictive systems, we collected relevant data in another institution as an external dataset. Consistent with our data, in the external cohort, we observed significant differences before and after interventional bronchoscopy. When verifying the prognostic value of the LASSO-based risk-score in external dataset, we proved its outstanding performance and verified significantly longer survival in patients with low-risk score, which further proved the excellent clinical values of this LASSO-based risk score system. Meanwhile, this risk score

system showed better performance in the external dataset as well when comparing with nomogram. Prospective clinical trials with a larger population were needed to evaluate the performance of this model.

Several limitations should be acknowledged. First, this was a retrospective study. The prognosis of patients' survival after bronchoscopy may be associated with several factors such as the patients' general status at the intervention, the histology of the tumor, the sites and length of bronchial or tracheal stenosis. Several clinical indicators to measure symptom relief and physiological status were not included in this study. Second, the sample size in our study was still not large enough although two institutions were included. In addition, it might become more accurate to measure the degree of stenosis by interventional bronchoscopy or tools based on artificial intelligence. More parameters may be considered for analysis and these findings need to be tested in a multi-center and prospective study based on a larger population.

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Footnote

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[org/10.21037/tlcr-21-301](https://dx.doi.org/10.21037/tlcr-21-301)). 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. This study was conducted consistent with the provisions of Declaration of Helsinki (as revised in 2013). Approval from the ethics committee of Shanghai Pulmonary Hospital was obtained (18Q016NJ) and individual consent for this retrospective analysis was waived.

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