Original Article

Risk factors and outcomes of bronchopleural fistula after bronchoplasty in patients with non-small cell lung cancer: a retrospective multivariate analysis

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Background: Bronchopleural fistula (BPF) is a rare but severe complication following bronchoplasty. Identification of the risk factors for the development of BPF after bronchoplasty may contribute to better perioperative management, thereby further improving the prognosis of these patients. However, few studies have focused on the risk factors for BPF after bronchoplasty. This study aimed to explore the risk factors and outcomes for BPF after bronchoplasty in patients with non-small cell lung cancer (NSCLC).

Methods: The data of NSCLC patients who underwent bronchoplasty between September 2005 and August 2020 in our institution were retrospectively reviewed. Detailed information on demographic characteristics, preoperative assessment, perioperative outcomes were collected from Western China Lung Cancer Database. The diagnosis of BPF was confirmed by bronchoscopy. Risk factors for BPF were assessed by univariate and multivariate logistic regression analysis.

Results: A total of 503 patients were included in this study, including 132 (26.2%) cases of broncho-vascular plasty, 340 (67.6%) cases of bronchial sleeve lobectomy, and 31 (6.2%) cases of bronchial wedge plasty. Among these patients, 16 (3.2%) developed postoperative BPF. Six patients with BPF died during hospital-stay, including two cases of severe hemoptysis, and four cases of pyothorax and respiratory failure caused by BPF. One of the other ten patients underwent reoperation. After univariate and multivariate logistic regression analysis, preoperative Charlson Comorbidity Index (CCI) ≥2 [odds ratio (OR) =5.120, 95% confidence interval (CI): 1.193–21.985, P=0.028], right middle and/or lower lobectomy (OR =4.840, 95% CI: 1.133–20.686, P=0.033), and residual tumor in the bronchial margin (OR =4.160, 95% CI: 1.106–15.644, P=0.035) were identified as independent risk factors for postoperative BPF.

Conclusions: Although complication rate of BPF after bronchoplasty is low, the mortality of BPF is high. Patients with higher CCI, those who undergo right middle and/or lower lobectomy, and those with residual tumor in the bronchial margin are at increased risk of BPF. This study highlights the importance of preoperative evaluation and good intraoperative management to prevent this catastrophic complication.

Keywords: Non-small cell lung cancer (NSCLC); bronchopleural fistula (BPF); bronchoplasty; risk factor; multivariate analysis

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Submitted Nov 08, 2021. Accepted for publication May 07, 2022.
doi: 10.21037/tlcr-22-272
View this article at: https://dx.doi.org/10.21037/tlcr-22-272

Introduction

Bronchopleural fistula (BPF) is a rare but severe complication after lung surgery, with an incidence ranged from 1.5% to 8.5% according to most reports (1-3). Although the incidence of BPF is low, it can result in catastrophic outcomes, with a mortality rate as high as 50% (4,5). Bronchoplasty is preferred to pneumonectomy for central lung cancer when feasible due to its preservation of more lung parenchyma and comparable long-term outcomes (6). Some studies have reported that compared with routine lobectomy, the incidence of BPF after bronchoplasty is higher (7,8). Several risk factors have been reported to be associated with BPF after lung surgery, such as diabetes mellitus (9-11), neoadjuvant therapy (11-15), right pneumonectomy, and right lower lobectomy (3,8,9,16-18). However, few studies have focused on the risk factors for BPF after bronchoplasty. The identification of risk factors of BPF after bronchoplasty could guide optimal peri-operative management and the eventual coverage of local flap.

The aim of this study was to identify the occurrence and the risk factors for BPF after bronchoplasty in non-small cell lung cancer (NSCLC) patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-272/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee on Biomedical Research, West China Hospital, Sichuan University (No. 2021-1101). The requirement for informed consent was waived for this single-center retrospective study. The data were obtained from the Western China Lung Cancer Database (WCLCD), which collected the data of lung cancer patients who underwent surgery at the Department of Thoracic Surgery, West China Hospital, Sichuan University since August, 2005.

Patients

All consecutive patients who underwent bronchoplasty for lung cancer between September 2005 and August 2020 were enrolled in this single-center, retrospective study. Patients who received video-assisted thoracic surgery (VATS) or open bronchoplasty combined with or without lobectomy, and systemic lymph node dissection were eligible for inclusion. The exclusion criteria were as follows: (I) patients who underwent bilateral lung surgery; and (II) patients who underwent previous ipsilateral pulmonary resection.

The data of the included patients were retrospectively retrieved from the WCLCD. We included information about demographic characteristics [age, gender, body mass index (BMI), smoking history, comorbidities, history of neoadjuvant chemotherapy], preoperative assessment (pulmonary function, laboratory examination), perioperative outcomes [surgical procedure, blood loss, transfusion, thoracic adhesion, residual tumor in the bronchial margin, diameter, histology, differentiation and pathological tumor-node-metastasis (p-TNM) stage of the tumor, postoperative complications], and other relevant information (length of hospital stay). Smoking history was quantified by using the smoking index (19). All patients' comorbidities (diabetes, dementia, coronary artery disease, chronic pulmonary disease and so on) were recorded and converted to the Charlson Comorbidity Index (CCI) (20). Since the included patients all have solid lung tumors, the CCI in this article does not calculate the 2 points for solid tumors. The p-TNM stages of all patients were converted to the 7th edition of TNM-staging classification for lung cancer.

Surgical technique

The detailed surgical technique of bronchoplasty has been described in our previous publications (21-24). For tumors that invaded the parenchyma, a lobectomy or pneumonectomy was performed according to the extent of tumor invasion, while for tumors that infiltrated only the bronchus, bronchial sleeve resection was performed without removing the parenchyma. In this cohort, wedge

bronchoplasty was selected if the tumor was located at the lobar bronchial orifice without invading the main bronchus, and sleeve bronchoplasty was selected when the tumor or lymph node invaded the spur or the main bronchus. Bronchial anastomosis of sleeve plasty was carried out using 3-0 Prolene stitch with a single running suture, and anastomosis of wedge plasty was routinely carried out using an interrupted suture. If the pulmonary vessels were affected by the tumor or metastatic lymph nodes, angioplasty was performed using 5-0 Prolene stitches. After bronchoplasty, the integrity of the anastomosis was checked by bronchoscopy and any secretion was removed. Water-sealed test was performed to check for air leaks. Any stenosis or defect detected by intraoperative bronchoscopy was immediately corrected.

All patients received routine subcutaneous heparin to prevent thrombosis and intravenous antibiotics for at least 3 days to prevent infection after bronchoplasty. The following criteria was met before the chest tubes could be removed: (I) chest X-ray showed that the lung was well expanded; (II) no air leakage; and (III) the drainage fluid was clear and the volume of drainage was less than 300 mL per 24 h.

The occurrence of BPF during postoperative hospitalization is the endpoint of this study. Also, we included in the analysis patients who were re-admitted because of BPF within 30 days after surgery. Routine bronchoscopy was performed on postoperative day 1 or 2 to clear the airway secretions. If there was atelectasis, suspected BPF, or persistent air leak, bronchoscopy was also promptly performed. The diagnosis of BPF was confirmed by bronchoscopy. Patients with suspected or confirmed postoperative BPF received immediate chest tube drainage to prevent aspiration to the contralateral lung. Anti-infective therapy was routinely used for all patients. For patients with severe pulmonary infection, completion pneumonectomy was performed.

Statistical analysis

SPSS software (version 24.0, IBM Corporation, Los Angeles, CA, USA) was used for statistical analysis. Missing data (less than 10%) was considered acceptable and filled in using the K-Nearest Neighbor (KNN) method (25). Continuous variables were represented as the mean ± standard deviation or median (interquartile range, IQR) accordingly, and compared using the student *t*-test or Mann-Whitney U test when appropriate. When comparing categorical variables, the χ^2 test or Fisher-exact test was used.

Variables with a P value <0.1 in the univariate analysis were included in the multivariate analysis. To test the independence of each risk factor and adjust for covariates (including age, gender, surgical procedure, and p-TNM stage), the statistically and clinically significant variables considered in the univariate analysis before and during the operation were analyzed using a multivariate logistic regression model with positive likelihood ratio selection. Finally, risk factors with a P value <0.05 in the multivariate analysis were considered as significant independent predictors.

Results

Patient characteristics

A total of 503 patients who underwent bronchoplasty were included in this study. No cases were excluded during the study period, and no patients were excluded based on the exclusion criteria. The total percentage of missing data was 5.9%, and we used the KNN method to fill in the missing values.

The baseline and perioperative characteristics are displayed in *Table 1*. The average age of the 503 included patients was 57.5±11.0 years, and there were 442 (87.9%) male patients. Furthermore, 393 (78.1%) patients had a history of smoking, and 296 (58.8%) patients had a smoking index higher than 400. In terms of comorbidities, 37 (7.4%) had diabetes, 93 (18.5%) had hypertension, and 82 (16.3%) had chronic obstructive pulmonary disease (COPD). After converting all complications into the CCI, there were 27 (5.4%) patients with CCI ≥2. Before surgery, a total of 31 (6.2%) patients underwent neoadjuvant therapy. Among them, 25 patients received chemotherapy, 1 radiotherapy, 2 targeted therapy, 2 chemotherapy combined with radiotherapy, and 1 case of chemotherapy combined with targeted therapy.

VATS was performed in 86 (17.1%) patients, open surgery was performed in 396 (78.7%) patients, and 21 (4.2%) patients were converted from VATS to open surgery. Left upper lobectomy was performed in 164 cases (32.6%), left lower lobectomy in 69 (13.7%), right upper lobectomy in 227 (45.1%), and right middle and/or lower lobectomy in 35 (7.0%) patients. Six patients underwent bronchoplasty without lobectomy. Four patients had sleeve pneumonectomy, including three on the left side and one on the right side. Broncho-vascular plasty was performed

Table 1 Patient characteristics

Characteristics	Numbers
Patients	
Age (years)	57.5±11.0
Sex, n (%)	
Female	61 (12.1)
Male	442 (87.9)
BMI (kg/m^2)	23.2±3.3
Smoking index, n (%)	
0	110 (21.9)
>0 and ≤400	97 (19.3)
>400	296 (58.8)
CCI, n (%)	
0	364 (72.4)
1	112 (22.3)
≥2	27 (5.4)
Diabetes mellitus, n (%)	
No	466 (92.6)
Yes	37 (7.4)
Hypertension, n (%)	
No	410 (81.5)
Yes	93 (18.5)
COPD, n (%)	
No	421 (83.7)
Yes	82 (16.3)
Chronic hepatitis B, n (%)	
No	494 (98.2)
Yes	9 (1.8)
Neoadjuvant therapy, n (%)	
No	472 (93.8)
Yes	31 (6.2)
Pulmonary function	
pre% FVC	100.9±16.9
pre% FEV1	86.6±16.2
Laboratory examination, n (%)	
HGB (g/L)	136.8±14.9
ALB (g/L)	41.3±3.7
Surgery	
Surgical approach, n (%)	
VATS	86 (17.1)
Open	417 (82.9)
Surgical procedure, n (%)	
LUL	164 (32.6)
LLL	69 (13.7)
RUL	227 (45.1)
RML and/or RLL	35 (7.0)
Others	8 (1.6)
Bronchoplasty, n (%)	
Broncho-vascular plasty	132 (26.2)
Bronchial sleeve resection	340 (67.6)
Bronchial wedge plasty	31 (6.2)
Extended resection, n (%)	
No	470 (93.4)
Yes	33 (6.6)
Additional pulmonary resection, n (%)	
No	448 (89.1)
Yes	55 (10.9)
Intra- and postoperative results	
Operative time (min)	201.0 (IQR, 166–250)
Median blood loss (mL)	140.0 (IQR, 100–200)
Transfusion, n (%)	
No	467 (92.8)
Yes	36 (7.2)
Pleural adhesion, n (%)	
No	364 (72.4)
Yes	139 (27.6)
Length of stay (day)	9.0 (IQR, 7.0–12.0)
Pathology	
Diameter (cm)	4.1±1.8
Histology, n (%)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Numbers
Squamous cell carcinoma	380 (75.5)
Adenocarcinoma	60 (11.9)
Others	63 (12.5)
Lymph node metastasis, n (%)	
No	224 (44.5)
Yes	279 (55.5)
Residual margin, n (%)	
No	469 (93.2)
Yes	34 (6.8)
p-TNM stage, n (%)	
I	151 (30.0)
II	164 (29.6)
III	181 (36.0)
IV	7 (1.4)

Data are presented as mean ± SD, median (IQR) or No. (%). BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; HGB, hemoglobin; ALB, albumin; VATS, video-assisted thoracic surgery; LUL, left upper lobe; LLL, left lower lobe; RUL, right left upper lobe; RML, right middle lobe; RLL, right lower lobe; SD, standard deviation; IQR, interquartile range.

in 132 (26.2%) patients, sleeve bronchoplasty without angioplasty was carried out in 340 (67.6%) patients, and wedge bronchoplasty was conducted in 31 (6.2%) patients. Extended resection occurred in 33 (6.6%) patients, including 14 cases of pericardectomy, nine cases of carina resection, two cases of aortic adventitia resection, three cases of partial left atrium resection, three cases of chest wall resection, one case of partial aortic resection, and one case of partial superior vena cava resection.

The median operative time was 201.0 min (IQR, 166–250 min). The median blood loss was 140.0 mL (IQR, 100–200 mL). Perioperative blood transfusion was required in 36 (7.2%) patients. There were 139 (27.6%) cases of severe thoracic adhesions (≥50%) found during the operation. The median hospital stay was 9.0 days (IQR, 7.0–12.0 days). Postoperative BPF occurred in 16 cases (3.2%).

The mean diameter of the tumors was 4.1±1.8 cm. According to the 7th edition of the TNM classification for lung cancer, there were 151, 164, 181, and seven patients in p-TNM stages I, II, III, and IV, respectively. The postoperative pathological results revealed 380 (75.5%) cases of squamous cell carcinoma, 60 (11.9%) cases of adenocarcinoma, and 63 (12.5%) cases of other types of tumors. Residual tumor in the bronchial margin occurred in 34 (6.8%) patients. Among these patients with residual tumor in the bronchial margin, 13 had N2 disease, 5 had N1 disease, and 16 had N0 disease.

Risk factors for BPF

Table 2 summarized the results of the univariate analysis. In the entire patient cohort, the univariate analysis indicated that preoperative CCI (P=0.015), operative time (P=0.033), blood loss (P=0.055), residual margin (P=0.018), intrathoracic adhesions (P=0.050) and surgical procedure (P=0.017) were potential risk factors for postoperative BPF. The multivariate analysis results were displayed in *Table 3*. After adjusting for covariates (including age, gender, surgical procedure, and p-TNM stage), preoperative CCI ≥2 [odds ratio (OR) =5.120, 95% confidence interval (CI): 1.193–21.985, P=0.028], right middle and/or lower lobectomy (OR =4.840, 95% CI: 1.133–20.686, P=0.033), and residual margin (OR =4.160, 95% CI: 1.106–15.644, P=0.035) were identified as independent risk factors for postoperative BPF.

The total percentage of missing data was 5.9%. Most common missing values included the lung function tests and lab test in the old medical records. We used the KNN method to fill in the missing values. In the sensitivity analysis, we compare the findings with and without KNN for imputation of missing data. Overall, the results of sensitivity analyses were consistent with those of primary analysis (Table S1).

The outcomes of BPF

Detailed information of the 16 patients who suffered BPF are listed in *Table 4*. The median postoperative hospital stay of these patients was 26 days (IQR, 16–37 days), which was significantly longer (P<0.001) than that of patients without BPF (9 days, IQR, 7–11 days). Among the patients who developed BPF, three patients underwent re-operation to clear the pyothorax and/or remove the residual lung. Six of these patients (37.5%) died during hospital-stay, including two cases of severe hemoptysis, and four cases of pyothorax and respiratory failure caused by BPF.

Table 2 Univariate analysis

Characteristics	No BPF (n=487)	BPF (n=16)	P value
Patients			
Age (years)	57.5±11.0	57.3±9.7	0.915
Sex, n (%)			
Female	60 (12.3)	1 (6.3)	0.706
Male	427 (87.7)	15 (93.7)	
BMI (kg/m^2)	23.2±3.3	22.5±3.6	0.396
Smoking index, n (%)			
0	107 (22.0)	3 (18.8)	0.829
>0 and ≤400	95 (19.5)	2 (12.5)	
>400	285 (58.5)	11 (68.8)	
CCI, n (%)			
0	355 (72.9)	9 (56.3)	0.015
1	109 (22.4)	3 (18.8)	
≥2	23 (4.7)	4 (25.0)	
Diabetes mellitus, n (%)			
No	452 (92.8)	14 (87.5)	0.332
Yes	35 (7.2)	2 (12.5)	
Hypertension, n (%)			
No	395 (81.1)	15 (13.0)	0.327
Yes	92 (18.9)	1 (6.3)	
COPD, n (%)			
No	408 (83.8)	13 (81.3)	0.733
Yes	79 (16.2)	3 (18.7)	
Chronic hepatitis B, n (%)			
No	479 (98.4)	15 (93.8)	0.254
Yes	8 (1.6)	1 (6.3)	
Neoadjuvant therapy, n (%)			
No	457 (93.8)	15 (93.7)	1.000
Yes	30 (6.2)	1 (6.3)	
Pulmonary function			
pre% FVC%	100.8±16.9	104.0±14.4	0.476
pre% FEV1	86.5±16.2	88.7±13.7	0.374
Laboratory examination			
HGB (g/L)	136.8±15.0	139.4±11.4	0.493
ALB (g/L)	41.3±3.7	42.5±3.3	0.194

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	No BPF (n=487)	BPF (n=16)	P value
Surgery			
Surgical approach, n (%)			
VATS	84 (17.2)	2 (12.5)	1.000
Open	403 (82.8)	14 (87.5)	
Surgical procedure, n (%)			
LUL	160 (32.9)	4 (25.0)	0.017
LLL	69 (14.2)	0 (0.0)	
RUL	219 (45.0)	7 (43.8)	
RML and/or RLL	31 (6.4)	5 (31.3)	
Others	8 (1.6)	0 (0.0)	
Bronchoplasty, n (%)			
Broncho-vascular plasty	127 (26.1)	5 (31.3)	0.833
Bronchial sleeve resection	330 (67.8)	10 (62.5)	
Bronchial wedge plasty	30 (6.2)	1 (6.3)	
Extended resection, n (%)			
No	455 (93.4)	15 (93.7)	1.000
Yes	32 (6.6)	1 (6.3)	
Additional pulmonary resection, n (%)			
No	435 (89.3)	13 (81.3)	0.402
Yes	52 (10.7)	3 (10.9)	
Duration of surgery (min)	200.0 (166.0–245.0)	250.0 (209.5–268.8)	0.033
Blood loss (mL)	134.0 (100.0–200.0)	200.0 (136.5–300.0)	0.055
Transfusion, n (%)			
No	454 (93.2)	14 (87.5)	0.307
Yes	33 (6.8)	2 (12.5)	
Pleural adhesion, n (%)			
No	356 (73.1)	8 (50.0)	0.050
Yes	131 (26.9)	8 (50.0)	
Length of stay (day)	9.0 (7.0–11.0)	26.5 (15.5–39.0)	<0.001
Pathology			
Diameter (cm)	4.1±1.9	4.1±1.7	0.922
Histology, n (%)			
Squamous cell carcinoma	366 (75.2)	14 (87.5)	0.453
Adenocarcinoma	60 (12.3)	0 (0.0)	
Others	61 (12.5)	2 (12.5)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	No BPF (n=487)	BPF (n=16)	P value
Lymph node metastasis, n (%)			
No	218 (44.8)	6 (37.5)	0.619
Yes	269 (55.2)	10 (62.5)	
Residual margin, n (%)			
No	457 (93.8)	12 (75.0)	0.018
Yes	30 (6.2)	4 (25.0)	
p-TNM stage, n (%)			
I	146 (30.0)	5 (31.3)	0.676
II	157 (32.2)	7 (43.8)	
III	177 (36.3)	4 (25.0)	
IV	7 (1.4)	0 (0.0)	

Data are presented as mean ± SD, median (IQR) or No. (%). BPF, bronchopleural fistula; BMI, body mass index; CCI, Charlson Comorbidity Index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; HGB, hemoglobin; ALB, albumin; VATS, video-assisted thoracic surgery; LU, left upper lobe; LLL, left lower lobe; RUL, right left upper lobe; RML, right middle lobe; RLL, right lower lobe; SD, standard deviation; IQR, interquartile range.

Table 3 Multivariate analysis

Risk factors	Multivariate analysis		
	OR	95% CI	P value
CCI (Ref =0)			
1	1.108	0.307–3.991	0.876
≥2	5.120	1.193–21.985	0.028
Operative time	1.003	0.995–1.011	0.489
Blood loss	1.001	0.999–1.002	0.434
Pleural adhesion (Ref =no)	2.353	0.799–6.929	0.121
Residual margin (Ref =no)	4.160	1.106–15.644	0.035
Surgical procedure (Ref =LUL)			
LLL	–	–	–
RUL	0.993	0.267–3.688	0.991
RML and/or RLL	4.840	1.133–20.686	0.033
Others	–	–	–

CCI, Charlson Comorbidity Index; LUL, left upper lobe; LLL, left lower lobe; RUL, right left upper lobe; RML, right middle lobe; RLL, right lower lobe; OR, odds ratio; CI, confidence interval.

Table 4 Detailed information of 16 patients with BPF

No.	Age (years)	Sex	Neoadjuvant therapy	Surgical approach	Surgical procedure	Bronchoplasty	Angioplasty	Histology	p-TNM stage	Reoperation	Outcomes
1	61	M	No	Open	LUL	Sleeve	No	LUSC	IIA	No	Died on POD 24
2	62	M	No	Open	RUL	Sleeve	No	Neuroendocrine tumor	IIIB	No	Died on POD 15
3	61	M	No	Open	RML & RLL	Sleeve	No	LUSC	IIIA	No	Discharged home
4	67	M	No	Open	LUL	Sleeve	Yes	LUSC	IIIA	No	Discharged home
5	66	M	No	Open	RLL	Sleeve	Yes	LUSC	IIA	No	Discharged home
6	70	M	Yes	VATS	RUL	Sleeve	No	Neuroendocrine tumor	IB	No	Died on POD 20
7	57	M	No	Open	RUL	Sleeve	No	LUSC	IIA	No	Discharged home
8	55	M	No	Open	RML & RLL	Sleeve	No	LUSC	IIA	No	Discharged home
9	47	M	No	Open	RUL	Sleeve	Yes	LUSC	IIA	Yes	Discharged home
10	52	M	No	Open	RUL	Sleeve	Yes	LUSC	IIIA	Yes	Died on POD 29
11	37	M	No	Open	LUL	Sleeve	Yes	LUSC	IB	No	Died on POD 9
12	54	M	No	VATS	RUL	Sleeve	No	LUSC	IIA	Yes	Died on POD 50
13	62	M	No	Open	RML	Sleeve	No	LUSC	IA	No	Discharged home
14	59	M	No	Open	RUL	Wedge	No	LUSC	IA	No	Discharged home
15	39	F	No	Open	RUL	Sleeve	No	LUSC	IIA	No	Discharged home
16	67	M	No	VATS	LUL	Sleeve	No	LUSC	IA	No	Discharged home

BPF, bronchopleural fistula; M/F, male/female; Open, open surgery; VATS, video-assisted thoracic surgery; LUL, left upper lobe; RUL, right left upper lobe; RML, right middle lobe; LLL, left lower lobe; RLL, right lower lobe; LUSC, lung squamous cell carcinoma; POD, postoperative day.

Discussion

The present study was designed to explore the risk factors for BPF after bronchoplasty. BPF is a severe complication of bronchoplasty, and identification of its risk factors can provide guidance for the perioperative management of these patients, thereby reducing the risk of BPF. A total of 503 patients were eventually included in this study. Of these patients, 16 (3.2%) developed postoperative BPF. Using multivariate analysis, preoperative CCI ≥2, right middle and/or lower lobe lung resection, and residual margin were identified as independent predictors of postoperative BPF.

Several studies have reported some risk factors related to the occurrence of BPF after lung surgery. Among them, the most reported risk factors include age at surgery (11,26), diabetes (9,11), COPD (27), neoadjuvant therapy (11-13), albumin level (8,28), as well as intraoperative factors such as residual margin (3), right pneumonectomy (8,17,18,29), and right middle and/or lower lobectomy (8,30). In this study, we used bronchoplasty patients as the study population, and obtained some of the same risk factors as those for the high incidence of BPF after pneumonectomy and lobectomy, such as residual margin and right middle and/or lower lobectomy. The above-mentioned reasons can be explained by the influence of the blood supply of the bronchial anastomosis or the stump. Several studies have reported that comorbidities such as diabetes can affect the blood supply to the bronchial anastomosis, delaying healing, and thus being highly associated with the occurrence of BPF (9,11). However, similar results were not observed in the present study. The common comorbidities of patients, such as diabetes, hypertension, COPD, and hepatitis, were not associated with the occurrence of BPF in the univariate analysis, which may be related to the strict preoperative glycemic control of patients (31). Interestingly, we scored comorbidities such as diabetes, COPD, and coronary arterial disease using the CCI, and found that CCI ≥2 was

an independent predictor of the occurrence of BPF after bronchoplasty. This suggests that preoperative CCI can help determine patient prognosis, and that patients with CCI scores of 2 or higher should have a reasonable strategy in place before surgery to prevent the development of BPF.

Right pneumonectomy and right lower and/or middle lobectomy are risk factors for BPF after bronchoplasty, and have been reported in several previous studies (3,8,9,16,17). In the present study, there were only four patients with pneumonectomy and only one with right pneumonectomy, so the association between right pneumonectomy and the occurrence of BPF was not explored. Moreover, the present study found that middle and/or lower lobectomy of the right lung was an independent predictive risk factor for bronchial BPF. Based on previous reports in the literature and our experience, there are several reasons that could explain this phenomenon. Firstly, for this group of patients undergoing bronchoplasty, our center routinely performed lymph node dissection, and the dissection of lymph nodes in the lower lobe of the right lung may affect the blood supply to some of the bronchial vessels (9,17). However, a previous study has reported that lymph node dissection does not result in higher morbidity or mortality after sleeve resection (32). Therefore, further research is needed on this issue. Secondly, the bronchi of the right lung are more vertical and wide compared to the left lung and are more likely to collect secretions postoperatively, thus making them more susceptible to infection and affecting the healing of the anastomosis or bronchial stump (9). In addition, it has been reported that unlike the left bronchus under the aortic arch, the right lower lobe bronchial anastomosis or stump is farther from the carina and is not covered by mediastinal tissue, making it easier to expose in the free space of the thorax (16,33).

In the present study, we also found that residual tumor in the bronchial margin is an independent predictor of BPF. Some previous reports have speculated that residual margin is associated with the occurrence of BPF, but due to the small sample size, no reliable conclusions were drawn (3,34). Although we attempted to avoid the occurrence of residual margin during the operation, there were still some patients whose residual margin could not be removed due to the large extent of tumor invasion. In this study, four of the 16 patients with BPF had residual margin, and the OR reached 4.160 in the multivariate analysis. We suggest that the tumor will affect the blood supply to the stump, and the growth of the tumor will also loosen the anastomosis at the stump, ultimately leading to the development of BPF.

Although the results of the multivariate analysis showed no correlation, we found that intrathoracic adhesions, prolonged operative time, and severe blood loss may be associated with a high incidence of BPF in the univariate analysis. To some extent, these results can also indicate their association with the occurrence of BPF. According to a previous report in the literature and our experience, severe intrathoracic adhesions, more blood loss, and prolonged operative time will increase the risk of surgical infection, affect the postoperative lung function and blood supply, and thus affect the healing of the bronchial anastomosis or stump (17).

A more common report in the previous literature is the high correlation between neoadjuvant radiotherapy and BPF (11-13,35). Some recent reports have found preoperative neoadjuvant therapy is a high-risk factor for BPF. They believe that induction therapy may impair bronchial healing due to microvascular injury and connective tissue proliferation. However, this topic remains controversial. Several studies have found that sleeve lobectomy for NSCLC could be safely performed after induction chemotherapy and radiotherapy, with mortality and airway complications similar to those in patients without pretreatment (36-39). In the present study, we included only 31 patients who received preoperative neoadjuvant treatments. Our results showed no correlation between neoadjuvant treatment and the occurrence of BPF. However, more research is needed on this topic in the future.

At present, the most common method used for the prevention of BPF is the bronchial stump coverage with a local tissue flap. Some authors reported that bronchial stump coverage is an effective method to prevent BPF and should be routinely used (27,40). However, Okuda and Di Maio *et al.* have reported that bronchial stump coverage has no significant effect on preventing BPF (4,16). Thus its role in preventing the development of BPF is still controversial, and prospective research is needed in the future. In our opinion, the current literature shows that bronchial stump coverage is useful in preventing BPF and should be use during bronchoplasty in patients with risk factors of BPF.

The current study still has some shortcomings that should be considered. Firstly, this is a retrospective study of a single-center cohort, and some of the patients in this study had incomplete data. The total percentage of missing data was 5.9%, and we used the KNN method to fill in the missing values. Secondly, the sample of patients who developed BPF in this study was only 16 cases; thus, future

studies with larger samples from multiple centers are still needed. Finally, the case data reviewed in this study spanned a long period. The current bronchoplasty technique has undergone major changes in surgical approach, surgical procedures, and neoadjuvant therapy compared to the past, which may also affect the results.

Conclusions

Patients with higher CCI, those who undergo right middle and/or lower lobectomy, and those with residual margin are at increased risk of BPF. These results emphasize the importance of preoperative evaluation and good intraoperative management to prevent this catastrophic complication.

Acknowledgments

The authors appreciate the academic support from the AME Thoracic Surgery Collaborative Group.
Funding: This study was supported by the 1.3.5 Project for Disciplines of Excellence (ZYJC18009), West China Hospital, Sichuan University.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-272/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-272/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-272/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). The study was approved by the Ethics Committee on Biomedical Research, West China Hospital, Sichuan University (No. 2021-1101), and individual consent for this retrospective analysis was waived.

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(English Language Editor: A. Kassem)

Cite this article as: Peng Z, Mei J, Liu C, Guo C, Gonzalez M, Bölükbas S, Voltolini L, Pu Q, Liu L. Risk factors and outcomes of bronchopleural fistula after bronchoplasty in patients with non-small cell lung cancer: a retrospective multivariate analysis. Transl Lung Cancer Res 2022;11(5):744-756. doi: 10.21037/tlcr-22-272