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The role of low-dose glucocorticoids in preventing bronchopleural fistula after bronchoplasty: a retrospective study

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Abstract

Objectives The aim of this study was to evaluate the clinical significance of early administration of low-dose corticosteroids after bronchoplasty, for the prevention of bronchopleural fistula (BPF).

Methods A total of 356 patients who underwent bronchoplasty in our hospital from 2019 to 2023 were retrospectively included. Univariate and multivariate logistic regression methods were used to determine the factors affecting the occurrence of BPF, and the significant factors were screened for Receiver Operating Characteristics (ROC) curves.

Results A total of 356 patients who underwent bronchoplasty were included in this study, 12 of whom developed BPF. Univariate and multivariate logistic regression analysis results showed that Preoperative serum albumin level (odds ratio (OR) = 0.64, 95% confidence interval (CI): 0.52–0.78, $P < 0.01$), low-dose glucocorticoid (OR = 0.11, 95% CI: 0.01–0.89, $P = 0.038$) were significant factors affecting postoperative BPF. Subsequently, the ROC curves of glucocorticoid and preoperative serum albumin level affecting the occurrence of BPF showed that low-dose glucocorticoids and preoperative albumin level were significantly correlated with the occurrence of BPF [Area Under Curves (AUC) = 0.681, AUC = 0.860], and the model had good prediction accuracy.

Conclusions Early use of low-dose glucocorticoids after bronchoplasty was associated with a reduced incidence of BPF, suggesting a potential role in preventing this complication. Preoperative serum albumin levels were identified as an independent risk factor for BPF, and it is recommended that a comprehensive assessment of the patient's nutritional status, including but not limited to serum albumin levels, be performed during preoperative management to optimize preoperative management and reduce the occurrence of BPF.

Keywords Bronchoplasty, Bronchopleural fistula (BPF), Low-dose glucocorticoids

Introduction

Breakthroughs in neoadjuvant therapy have provided a new treatment option for many patients with locally advanced lung cancer. Bronchoplasty is usually required for the complete removal of the tumor and the preservation of maximum lung function, especially for central lung cancers that are located in the bronchobronchial opening, protrusion, or with hilar lymph node enlargement and calcification. Bronchoplasty is a technique used to protect lung function in patients with central airway

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tumors. This usually involves the "sleeve" technique or annular excision of the airway, with initial reconstruction of the remaining uninvolved bronchi and lungs. This technique is an advance in thoracic surgery for central airway tumors that can preserve lung function and avoid total pneumonectomy [1, 2].

Several studies have reported a higher incidence of BPF with bronchoplasty compared with conventional lobectomy. This is usually due to the complexity of the bronchotomy and reconstruction process, which can lead to infection, ischemia, and poor healing. Conventional lobectomy is usually performed by cutting and stapling, which is relatively simple and reduces surgical complexity and the risk of associated complications [3]. As early as 1975, Rendinad et al. proposed that bronchial protection with pedicled muscle flaps and postoperative use of glucocorticoids were key factors in the success of airway reconstruction surgery [4]. In a large number of subsequent studies, many scholars have confirmed that pericardial fat pad and pedicled muscle flap covering bronchial stump can reduce the incidence of BPF [5, 6]. Since then, risk factors related to BPF, such as diabetes mellitus, neoadjuvant therapy, pneumonectomy, and preoperative low serum albumin, have also been shown to be related to the occurrence of BPF [7–10].

However, the use of glucocorticoids in the perioperative period has been controversial. Some researchers believe that glucocorticoids can jeopardize the bronchial healing process, and after lung transplantation, researchers usually delay glucocorticoid therapy until 2 to 3 weeks after surgery, when treatment is considered safe for airway healing [11–13]. Some opposing researchers believe that glucocorticoids can reduce edema and inflammation around the anastomosis, and play a positive role in the healing of bronchial anastomosis [14–16]. Therefore, the safety and effectiveness of glucocorticoids in the prevention of BPF need to be further confirmed. We reviewed our experience with post-bronchoplasty management to evaluate the clinical significance of early use of low-dose glucocorticoids after bronchoplasty for the prevention of BPF.

Methods

The study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the Ethics Review Committee of the Third Affiliated Hospital of Kunming Medical University (No. SLKYLX2023-212), which waived the requirement for informed consent as it was a retrospective study.

The retrospective study focused on a total of 387 lung cancer patients who underwent bronchoplasty at the Third Affiliated Hospital of Kunming Medical University between January 2019 and September 2023. Our inclusion criteria were: patients undergoing VATS or open bronchoplasty, with or without pulmonary lobectomy. Exclusion criteria were patients who underwent ipsilateral or bilateral lung resection without bronchoplasty. According to the inclusion criteria and exclusion criteria, 356 patients were finally eligible, including 12 patients with postoperative BPF and 344 patients without BPF. We collected information on demographic characteristics (sex, age, body mass index, history of smoking, alcohol consumption, history of cardiovascular disease, history of neoadjuvant therapy, hypertension, diabetes, history of other malignancies), preoperative assessment (lung function, serum albumin level), procedure, pathological type, TNM stage, glucocorticoid use, etc.

Preoperative management

The patients included in the study underwent a preparation regimen two days before surgery. They routinely inhaled budesonide for airway management, underwent back patting exercises, and completed cough and other pulmonary rehabilitation training.

Procedure

All procedures were performed by the same team through standard single-hole thoracoscopy or small anterolateral incisions The anastomosis was performed by manual continuous suture of the bronchial anastomosis or stump. The surgical procedures were sleeve lobectomy, lobectomy, pneumonectomy, and carina/reconstruction.

For tumors invading the lung parenchyma, lobectomy or pneumonectomy were selected according to the degree of tumor invasion and the frozen pathology of the bronchial stump during the operation. For tumors that only invaded the bronchus, bronchial sleeve resection that preserved the lung parenchyma was chosen. If the tumor was located in the lobar bronchial opening and did not invade the main bronchus, wedge bronchoplasty or sleeve bronchoplasty was selected based on the freezing results of the bronchial stump during surgery. All bronchoplasty procedures were performed with continuous suture with 3–0 prolene thread. After the suture was completed, the bronchoscope was used to enter the lumen to check whether the sutures were sheath and loose, and the secretions in the airway were removed. The sealing test was then performed with 25 cm H_2O pressure.

Postoperative management

In this study, all patients received intravenous antibiotics for at least three days postoperatively to prevent infection and subcutaneous low-molecular-weight heparin injections during hospitalization to prevent thrombosis. For patients receiving low-dose glucocorticoid therapy,

intravenous methylprednisolone (40 mg) was administered starting at 9 a.m. on the first postoperative day and continued daily for three days. The decision to use low-dose glucocorticoids was made by our treatment team based on long-term clinical experience and individual patient factors. These factors included preoperative nutritional status (e.g., serum albumin levels, BMI), the complexity of the bronchoplasty, and the presence of high-risk comorbidities (e.g., tuberculosis, diabetes). Patients with these high-risk comorbidities were more likely to receive low-dose glucocorticoids to mitigate postoperative inflammatory responses and reduce the risk of BPF. The dosage of 40 mg/day of methylprednisolone was selected based on clinical studies by Rendina et al. [4], which demonstrated that this dose effectively suppresses inflammation without increasing the risk of infection. To ensure treatment safety, daily laboratory tests were conducted to monitor patient indicators, and postoperative status was assessed using chest X-rays. Before removing the chest tube, the following conditions were required to be met: (1) Chest X-ray indicates that the lung review is good; (2) No air bubbles overflow when coughing.

A bronchoscope was used on the first, third, and seventh day after surgery to check the healing of the patient's anastomosis and remove airway secretions. When patients present with unexplained fever, increased cough and sputum, and persistent air leakage, the occurrence of BPF should be highly suspected and confirmed by bronchoscopy combined with chest Computed Tomography (CT) examination. Patients with definite BPF were treated with closed thoracic drainage, antibiotics and anti-infection treatment, and the healthy side was kept elevated to prevent the pus from flowing back to the healthy lung and causing infection of both lungs. According to the general condition of the patient and the size of the fistula, bronchoscopic stent closure or thoracotomy was selected.

Statistical analysis

Data analysis was conducted using R software with autoReg package (version 4.0.3; http://www.r-project.org) as well as SPSS software (version 21; IBM Corp, Armonk, NY, USA). The categorized data were presented as numbers and percentages. Univariate and multivariate logistic regression analyses were used to determine the effect factors. The variables with p-values < 0.05 in the multivariate regression analysis were used to develop Receiver operating characteristic(ROC) curves. ROC curves were adopted to predict the accuracy. The higher the area under the curves (AUC) was, the better the accuracy would be. AUC values vary from 0.5 to 1.0, where 0.5 represents random chance, and 1.0 represents full compliance.

Results

Clinical characteristics

The characteristics of clinical samples are shown in Table 1. A total of 356 patients with a mean age of 58.63 ± 8.77 years underwent bronchoplasty were included in the study cohort. There were 338 males (94.94%) and 18 females (5.06%). In terms of comorbidities, there were 51 cases of hypertension (14.33%), 16 cases of coronary heart disease (4.49%), 18 cases of diabetes (5.06%), 9 cases of malignant tumor history (2.53%), 53 cases (14.89%) received neoadjuvant therapy, of which 15 cases received chemotherapy combined with immunotherapy (albumin combined with paclitaxel + carboplatin + tillizumab). 38 patients received chemotherapy alone (albumin combined with paclitaxel + carboplatin). In addition, 253 cases (71.07%) had a history of smoking and 104 cases (29.41%) had a history of drinking. Video-assisted thoracic surgery [VATS] was performed in 115 patients (32.3%), and open-chest surgery was performed in 241 patients (67.7%). 94 patients underwent left upper lobe resection (26.40%), 46 patients (12.92%) underwent left lower lobe resection, 14 patients (3.93%) underwent left total lung resection, 108 patients (30.34) underwent right upper lobe resection, and 24 patients (6.74) underwent right middle lobe resection. Right lower lung lobectomy was performed in 53 patients (14.89), and in 17 patients (4.78%), the right middle and lower lung lobectomy was performed. The median operative time was 192.19 ± 74.88 min. Sleeve lobectomy (41.01%) was performed in 146 cases (41.01%) and cuneiform bronchoplasty (58.99%) was performed in 210 cases (58.99%). There were 79 patients (22.19%) in stage I, 121 patients (32.99%) in stage II, and 154 patients (43.26%) in stage III. Postoperative BPF occurred in 12 cases (3.37%), of which 1 case (8.33%) was treated with low-dose glucocorticoid, and 11 cases (91.67%) were not treated with low-dose glucocorticoid. Among the 12 patients, the specific days when BPF occurred were 6, 11, 12, 15, 16, 17, 17, 23, 24, 42, 45, and 48 days, with a median time of 17 days.

The difference analysis of 22 variables showed that BPF had significant differences in BMI ($P = 0.004$), preoperative albumin level ($P < 0.01$), tumor stage ($P = 0.002$), and glucocorticoid use ($P = 0.013$).

Explicit comparisom of steroid use

The group receiving low-dose glucocorticoids had a significantly lower incidence of BPF (0.5%) compared to the group that did not receive glucocorticoids (5.6%). This difference suggests that the use of low-dose glucocorticoids may play a protective role in preventing BPF by

Table 1 Clinical Characteristics of the Patients

Variable	Total ($n=356$)	No BPF ($n=344$)	BPF ($n=12$)	P
Age, Mean ± SD	58.63 ± 8.77	58.52 ± 8.67	61.75 ± 11.50	0.211
BMI, Mean ± SD	22.23 ± 3.03	22.28 ± 3.05	20.63 ± 1.59	0.004
Operation duration min, Mean ± SD	192.19 ± 74.88	192.73 ± 75.42	176.67 ± 57.66	0.466
FEV1/FVC, Mean ± SD	80.88 ± 8.35	80.86 ± 8.35	81.35 ± 8.94	0.843
Albumin, Mean ± SD	45.55 ± 4.30	45.77 ± 4.10	39.27 ± 5.41	< .001
Sex, n (%)				1.000
Female	18 (5.06)	18 (5.23)	0 (0.00)	
Male	338 (94.94)	326 (94.77)	12 (100.00)	
Hypertension, n (%)				0.854
No	305 (85.67)	294 (85.47)	11 (91.67)	
Yes	51 (14.33)	50 (14.53)	1 (8.33)	
CHD, n (%)				1.000
No	340 (95.51)	328 (95.35)	12 (100.00)	
Yes	16 (4.49)	16 (4.65)	0 (0.00)	
DM, n (%)				0.118
No	338 (94.94)	328 (95.35)	10 (83.33)	
Yes	18 (5.06)	16 (4.65)	2 (16.67)	
Tumor history, n (%)				1.000
No	347 (97.47)	335 (97.38)	12 (100.00)	
Yes	9 (2.53)	9 (2.62)	0 (0.00)	
Smoking history, n (%)				0.985
No	103 (28.93)	99 (28.78)	4 (33.33)	
Yes	253 (71.07)	245 (71.22)	8 (66.67)	
Drinking history, n (%)				0.516
No	252 (70.79)	242 (70.35)	10 (83.33)	
Yes	104 (29.21)	102 (29.65)	2 (16.67)	
Staging of tumor, n (%)				0.002
Benign	2 (0.56)	0 (0.00)	2 (16.67)	
I	79 (22.19)	77 (22.38)	2 (16.67)	
II	121 (33.99)	117 (34.01)	4 (33.33)	
III	154 (43.26)	150 (43.60)	4 (33.33)	
Neoadjuvant therapy, n (%)				0.813
No	303 (85.11)	292 (84.88)	11 (91.67)	
Yes	53 (14.89)	52 (15.12)	1 (8.33)	
Neoadjuvant chemotherapy, n (%)				0.853
No	318 (89.33)	308 (89.53)	10 (83.33)	
Yes	38 (10.67)	36 (10.47)	2 (16.67)	
Neoadjuvant immunotherapy combined with chemotherapy, n (%)				1.000
No	341	329	11	
Yes	15	15	1	
Surgical procedure, n (%)				0.061
LUL	94 (26.40)	90 (26.16)	4 (33.33)	
LLL	46 (12.92)	45 (13.08)	1 (8.33)	
LP	14 (3.93)	12 (3.49)	2 (16.67)	
RUL	108 (30.34)	105 (30.52)	3 (25.00)	
RML	24 (6.74)	24 (6.98)	0	
RLL	53 (14.89)	53 (15.41)	0	
RMLL	17 (4.78)	15 (4.36)	2 (16.67)	
Pathological type, n (%)				0.156

Table 1 (continued)

Variable	Total ($n=356$)	No BPF ($n=344$)	BPF ($n=12$)	*P*
Adenocarcinoma	27 (7.58)	26 (7.56)	1 (8.33)	
Others	22 (6.18)	20 (5.81)	2 (16.67)	
Squamous cell carcinoma	307 (86.24)	298 (86.63)	9 (75.00)	
Operation methods, n (%)				1.000
VATS	115 (32.3)	111 (32.27)	4 (33.33)	
Open	241 (67.7)	233 (67.73)	8 (66.67)	
Anastomotic methods, n (%)				0.801
Sleeve lobectomy	146 (41.01)	142 (41.28)	4 (33.33)	
Bronchial wedge plasty	210 (58.99)	202 (58.72)	8 (66.67)	
Broncho-vascular plasty Sleeve, n (%)				1.000
No	293 (82.3)	283 (82.27)	10 (83.33)	
Yes	63 (17.7)	61 (17.73)	2 (16.67)	
Glucocorticoid, n (%)				0.013
No	202 (56.74)	191 (55.52)	11 (91.67)	
Yes	154 (43.26)	153 (44.48)	1 (8.33)	

BMI body mass index, *DM* Diabetes mellitus, *VATS* video-assisted thoracic surgery, *CHD* Coronary heart disease, *FVC* forced vital capacity, *FEV1* forced expiratory volume in one second, *LUL* left upper lobe, *LLL* left lower lobe, *LP* left pneumonectomy, *RUL* right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *RMLL* right lung middle and lower lobe, *BPF* bronchopleural fistula

reducing inflammation and promoting better healing of the bronchial anastomosis.

Univariate and multifactorial analysis of BPF

Table 2 summarizes the influence of various factors on BPF. The results of the univariate regression analysis showed that BMI, preoperative serum albumin level, diabetes and glucocorticoids were potential factors affecting the occurrence of BPF, and then there were significant differences ($P<0.05$) were included in the multivariate logistics regression analysis, The results are shown in Table 3, where preoperative low albumin (OR: 0.64 95%CI: 0.52–0.78 $P<0.001$) and glucocorticoids (OR: 0.11, 95%CI: 0.01–0.89, $P=0.038$) were identified as independent significant factors affecting the occurrence of postoperative BPF.

ROC curves were constructed for analysis

The ROC curve was generated based on the significant factors ($P<0.05$) identified in the univariate regression analysis of BPF occurrence. Figure 1 depicts the impact of preoperative serum albumin levels and low-doses of glucocorticoids on the incidence of BPF. As illustrated in Fig. 1, both preoperative albumin levels and low-dose glucocorticoids were found to be highly accurate predictors of BPF (AUC=0.892). Then, the preoperative albumin level and low-dose glucocorticoid models were established. As can be seen from Figs. 2 and 3, low-dose glucocorticoids and preoperative albumin levels have a great influence on the occurrence of BPF (AUC=0.681, AUC=0.860), and the model has a good prediction accuracy. In this study, the prediction accuracy of preoperative albumin level was low, while the prediction accuracy of BPF was high.

Discussion

BPF is one of the most serious complications after pulmonary surgery. According to most research reports, its incidence is 0% – 12% and mortality is as high as 50% [17–19], which seriously threatens the life safety of patients. Good perioperative management helps to prevent the occurrence of BPF. In this study, 356 patients were eventually included, among which 12 patients developed BPF (3%). Out of those, 1 patient with low-dose glucocorticoid developed BPF, and 11 patients without glucocorticoid developed BPF. Further analysis was made using the AUC curves. There was a significant correlation between the low–dose glucocorticoids and the occurrence of BPF.

How can BPF be prevented? As early as the 1980s, Cooper et al. proposed that BPF could be effectively prevented by wrapping bronchopleural anastomosis with greater omentum based on their early experimental work [20]. In a subsequent prospective randomized controlled trial in patients with diabetic pneumonectomy, Sfyridis et al.'s results showed a significant reduction in BPF risk and empyema in patients with flaps [6]. In an animal study, Carbognani et al. performed immunohistological analysis and comparison of intercostal muscle, diaphragmatic flap, and pericardial fat pad, showing that all three methods have the ability to regenerate blood vessels [21]. Shoji et al. also demonstrated that pericardial fat pads

Table 2 Univariate logistic regression for the effect factors of BPF

Variables	Beta	S.E	Z	*P*	OR (95%CI)
Age	0.05	0.04	1.26	0.208	1.05 (0.97—1.13)
BMI	−0.20	0.11	−1.84	0.066	0.81 (0.66—1.01)
Operation duration, min	−0.00	0.00	−0.73	0.464	1.00 (0.99—1.01)
FEV1/FVC	0.01	0.04	0.20	0.842	1.01 (0.94—1.08)
Albumin	−0.45	0.10	−4.38	< .001	0.64 (0.52—0.78)
Sex					
Female					1.00 (Reference)
Male	15.26	1537.40	0.01	0.992	4,257,010.87 (0.00—Inf)
Neoadjuvant therapy					
No					1.00 (Reference)
Yes	−0.67	1.06	−0.64	0.524	0.51 (0.06—4.04)
Hypertension					
No					1.00 (Reference)
Yes	−0.63	1.06	−0.59	0.553	0.53 (0.07—4.23)
CHD					
No					1.00 (Reference)
Yes	−15.26	1630.66	−0.01	0.993	0.00 (0.00—Inf)
DM					
No					1.00 (Reference)
Yes	1.41	0.82	1.73	0.084	4.10 (0.83—20.29)
Tumor history					
No					1.00 (Reference)
Yes	−14.24	1318.73	−0.01	0.991	0.00 (0.00—Inf)
Smoking history					
No					1.00 (Reference)
Yes	−0.21	0.62	−0.34	0.733	0.81 (0.24—2.74)
Drinking history					
No					1.00 (Reference)
Yes	−0.75	0.78	−0.95	0.341	0.47 (0.10—2.20)
Staging of tumor					
Benign					1.00 (Reference)
I	−20.22	1696.73	−0.01	0.990	0.00 (0.00—Inf)
II	−19.94	1696.73	−0.01	0.991	0.00 (0.00—Inf)
III	−20.19	1696.73	−0.01	0.991	0.00 (0.00—Inf)
Pathological type					
Adenocarcinoma					1.00 (Reference)
Others	0.96	1.26	0.76	0.448	2.60 (0.22—30.75)
Squamous cell carcinoma	−0.24	1.07	−0.23	0.822	0.79 (0.10—6.44)
Operation method					
VATS					1.00 (Reference)
Open	−0.05	0.62	−0.08	0.938	0.95 (0.28—3.23)
Anastomotic methods					
Sleeve lobectomy					1.00 (Reference)
Bronchial wedge plasty	0.34	0.62	0.55	0.584	1.41 (0.42—4.76)
Broncho-vascular plasty Sleeve					
No					1.00 (Reference)
Yes	−0.07	0.79	−0.10	0.924	0.93 (0.20—4.34)
Glucocorticoid					
No					1.00 (Reference)
Yes	−2.18	1.05	−2.07	0.038	0.11 (0.01—0.89)

BMI body mass index, *DM* Diabetes mellitus, *CHD* Coronary heart disease, *FVC* forced vital capacity, *FEV1* forced expiratory volume in one second, *VATS* video-assisted thoracic surgery, *CI* confidence interval, *OR* odds ratio

Table 3 Multivariate logistic regression for the effect factors of BPF

Variables	Beta	S.E	Z	*P*	OR (95%CI)
Albumin	−0.48	0.12	−4.09	< .001	0.62 (0.49—0.78)
Glucocorticoid					
No					1.00 (Reference)
Yes	−2.48	1.10	−2.26	0.024	0.08 (0.01—0.72)

CI confidence interval, *OR* odds ratio

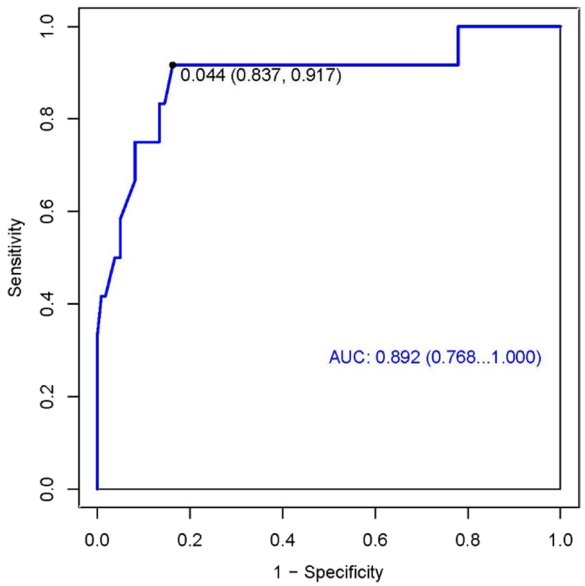

Fig. 1 ROC curve for predicting the risk of BPF after bronchoplasty. This ROC curve was generated to evaluate the predictive ability of certain factors for the occurrence of BPF. The area under the curve (AUC) is 0.892 (95% CI: 0.768 −1.000), indicating a relatively high discriminatory power. The optimal cut-off value is 0.044, with a sensitivity of 0.837 and a specificity of 0.917

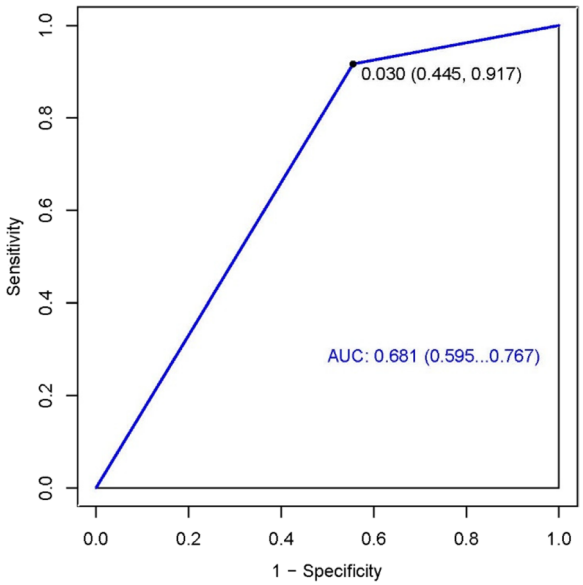

Fig. 2 ROC curves for the glucocorticoid. The AUC is 0.661 (95% CI: 0.595—0.767). The optimal cut-off value is 0.030, with a sensitivity of 0.445 and a specificity of 0.917

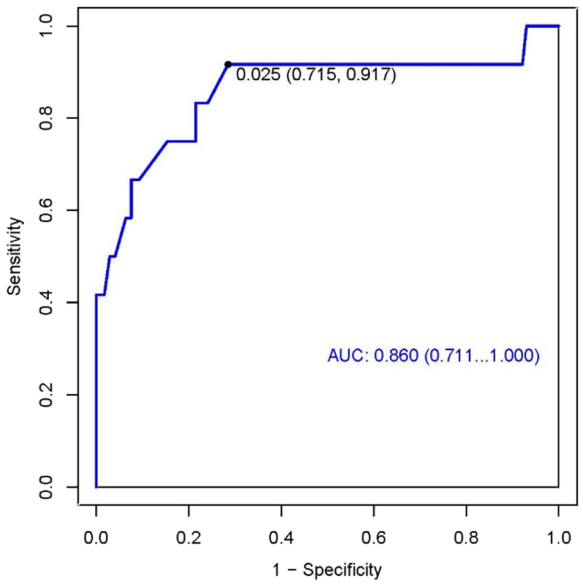

Fig. 3 ROC curves for the albumin. The AUC is 0.860 (95% CI: 0.711—1.000). The optimal cut-off value is 0.026, with a sensitivity of 0.715 and a specificity of 0.917

can produce angiogenic cytokines within seven days after surgery and play an important role in neovascularization at bronchial anastomosis [5]. These studies are based on providing new blood vessels to the bronchial anastomosis through autologous materials to promote its healing.

The earliest application of glucocorticoids in lung surgery can be traced back to the period of the rise of lung transplantation. Since lung transplantation requires the long-term anti-rejection effect of glucocorticoids, the safety of glucocorticoids after lung transplantation has attracted the attention of many researchers. Some early researchers believed that glucocorticoids could jeopardize the process of bronchial healing [22]. Fell et al. proposed that the use of corticosteroid hormones after airway reconstruction surgery could hinder the healing of bronchial anastomoses [23]. Sato et al.'s report also included corticosteroid use as a risk factor for BPF [24], contrary to our findings that the incidence of postoperative BPF was much lower in patients using low-dose corticosteroids than in patients not using corticosteroids (0.5% VS 5.6%).

Throughout the previous studies, especially in the period when lung transplantation was prevalent, most researchers took the non-use of glucocorticoids during

the perioperative period as the basis for the success of lung transplantation. Nevertheless, Calhoon and Novick and colleagues reported a series of lung transplant patients treated with glucocorticoids and found no broncho-related complications [25, 26]. In an animal experiment with dogs, Pinsker and colleagues found that glucocorticoids reduced the degree of inflammatory changes at the site of the anastomosis [27]. Additionally, in an earlier prospective study of sleeve lobectomy, Rendina et al. reported that bronchial healing was not impaired with either long-term or short-term low-dose glucocorticoid therapy [4]. We are excited that these findings also seem to support our observation that low-doses of glucocorticoids reduce edema and inflammation around the anastomosis and have a positive effect on bronchial healing.

Through bronchoscopy of patients with BPF, we found that a large number of avascular necrosis and secretions were often accumulated and attached at the fistula opening, accompanied by serious endotracheal mucosal edema. Endotracheal mucosa is the weakest and most sensitive part of the bronchial wall, and trachea reconstruction means the interruption of blood flow in the distal bronchial mucosa. Revascularization from surrounding tissue is required. Otherwise, as ischemia progresses, the bronchial wall will show signs of connective tissue softening and necrosis, and then evolve into mediastinal or pleural cavity perforation, resulting in BPF. However, mucosal edema is very common in the early days after airway reconstruction. Rendina et al. suggested that edema could cause the sutures to loosen and force the sutures to create a "cutting effect" to cut the bronchial wall into the lumen [4]. Ludwig and colleagues divided the healing of bronchial anastomosis after sleeve lobectomy into five classes [28], and in our study, patients treated with glucocorticoids had more significant anastomotic healing grades than those not treated with glucocorticoids, and showed less bronchial mucosal edema and better bronchial healing, which seems to further indicate the positive effect of low-doses of glucocorticoids in promoting bronchial healing.

In addition, studies have shown that the occurrence of BPF is also closely related to inflammation. Ischemia reperfusion injury after airway reconstruction can release a large number of inflammatory factors, and long-term and repeated inflammatory stimulation of the anastomosis will cause bronchopleural mucosal ischemia and necrosis, leading to the occurrence of BPF [29]. Pinsker et al. demonstrated that glucocorticoids may play a positive role in the healing of bronchial resists by inhibiting vascular rejection and reducing bronchial ischemia by limiting reperfusion injury [27]. Secondly, the powerful anti-inflammatory effect of glucocorticoids can also reduce tissue congestion, reduce capillary permeability, relieve exudation and edema, thereby reducing the retention of airway secretions, and promote lung reexpansion, providing a good healing environment for the bronchial anastomosis. In a word, mucosal edema, inflammation and ischemic reaction around the anastomosis after airway reconstruction are the main reasons for the poor healing of the anastomosis and the occurrence of BPF.

In this study, only 1 patient developed BPF after taking a low-dose of glucocorticoids. The patient developed recurrent cough with high fever 42 days after bronchoplasty and was diagnosed with BPF with coronavirus disease 2019 (COVID-19) upon return to the hospital. Despite aggressive treatment, the patient unfortunately passed away due to respiratory failure one week after the diagnosis of the BPF. After carefully reviewing the patient's medical experience, we found that due to the invasion of the main artery of the right lung and the right main bronchus during the operation, we transplanted the pericardial wall of the patient to repair the pulmonary artery vessels, and performed sleeve resection of the upper lobe of the right lung. After the operation, low-dose glucocorticoid therapy was given for 3 days. A series of bronchoscopies since then showed good healing. Whether COVID-19 impaired the healing of bronchial anastomoses is unknown. However, it is certain that the patient did not show significant poor healing of the bronchial anastomosis in the early bronchoscopy report.

It is worth mentioning that according to Algar and colleagues, BPF can be divided into early BPF and late BPF according to the occurrence time. BPF occurring within one month after surgery is defined as early BPF, after this time it is called late BPF [30]. In our study, only 1 patients receiving low-dose glucocorticoids developed BPF at 42 days postoperatively, while 8 of those not receiving low-dose glucocorticoids developed BPF at 30 days postoperatively. Of course, due to the limited sample size, we cannot fully conclude that there is a correlation between the two, but it seems to give us an important signal that low-doses of glucocorticoids play an important role in the early healing of bronchial anastomoses.

It is well known that the use of glucocorticoids can also increase the risk of postoperative infection, delay wound healing, gastrointestinal bleeding, hypertension, hyperglycemia and other adverse reactions. Nevertheless, most studies have shown that low-dose glucocorticoid use has no significant effect on surgical incision infection, delayed wound healing, and anastomotic fistula, and there is no dose correlation. However, it is worth noting that the use of large doses and long periods of glucocorticoids in the perioperative period should still be avoided to reduce the risk of adverse reactions [31].

In addition, in a study using glucocorticoid and azathioprine to treat bronchial anastomotic healing, Lima et al. demonstrated a reduction in bronchial anastomotic strength, which may indicate that multiple immunosuppressants are adverse to bronchial healing [32]. Therefore, further research is needed to confirm whether the safety of glucocorticoids can be guaranteed in patients who received neoadjuvant therapy including immunosuppressants before.

Although some studies suggest that glucocorticoids may increase the risk of BPF, these conclusions are often based on high-dose or long-term use [24]. Our short-term, low-dose regimen (3 days) demonstrated good safety, consistent with the findings of Toner et al. in their meta-analysis, which concluded that perioperative low-dose glucocorticoids do not increase the risk of infection or anastomotic leakage [31].

On the other hand, we found a significant correlation between the occurrence of BPF and preoperative low serum albumin levels, which is consistent with the results of Mazzella et al. [33]. This provides additional basis for the premise that for patients with poor preoperative nutritional status, nutritional assessment should be given sufficient attention in the perioperative period.

The benefits of glucocorticoids may stem from their dual regulation of the anastomotic microenvironment: (1). Reduction of Edema and Inflammation: Early postoperative anastomotic edema may lead to local ischemia through mechanical compression. Glucocorticoids alleviate edema by reducing capillary permeability and inflammatory exudation; (2) Promotion of Angiogenesis: Animal studies have shown that glucocorticoids upregulate the expression of vascular endothelial growth factor (VEGF), accelerating neovascularization at the anastomosis [27]. This mechanism aligns with the low BPF incidence observed in our study (0.5% vs. 5.6%); (3) Balancing Immunosuppression and Healing: While high-dose glucocorticoids may delay wound healing, low-dose therapy (as in our study) suppresses excessive inflammation while preserving key processes such as fibroblast proliferation and collagen deposition [32].

Regrettably, in recent years, there has been a notable scarcity of research progress regarding the role of glucocorticoids in bronchial healing, with most landmark studies concentrated in the last century. Despite our extensive literature search to identify recent studies in this field, we found that the available research protocols and results remain extremely limited. This situation not only highlights the relative stagnation of this research area in recent years but also underscores the innovation and forward-looking nature of our study design. Although these early studies are dated, they have laid a solid foundation for the role of glucocorticoids in airway healing. Their value should not be overlooked, as they provide essential theoretical support for subsequent research.

Our study has certain limitations. First, this is a single-center retrospective study, and there may be biases in the selection of patients. Second, the use of low-dose glucocorticoids in our study was not randomly assigned but rather based on the clinical judgment of the treatment team. This decision took into account the individual risk profiles of the patients and the complexity of the surgical procedures. Although this approach may introduce some bias, it reflects the real-world clinical scenario, where treatment decisions are often tailored to individual patient needs. Future studies should further clarify the optimal use of glucocorticoids in this context through prospective designs.

Lastly, there are significant differences in the pharmacological effects of various glucocorticoids. Currently, there is no unified guideline or consensus on the selection and use of glucocorticoids. Specifically, questions regarding which type of glucocorticoid is most appropriate, the optimal dosage, timing of administration, duration of use, and target patient population remain to be addressed. These issues need to be further explored and clarified through multicenter prospective randomized studies.

Conclusions

Early use of low-dose glucocorticoids after bronchoplasty was associated with a reduced incidence of BPF, suggesting a potential role in preventing this complication. Preoperative serum albumin levels were identified as an independent risk factor for BPF, and it is recommended that a comprehensive assessment of the patient's nutritional status, including but not limited to serum albumin levels, be performed during preoperative management to optimize preoperative management and reduce the occurrence of BPF.

Abbreviations

BPF	Bronchopleural fistula
ROC	Receiver operating characteristics
OR	Odds ratio
CI	Confidence interval
AUC	Area under curves
BMI	Body mass index
DM	Diabetes mellitus
CHD	Coronary heart disease
FVC	Forced vital capacity
FEV1	Forced expiratory volume in one second

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Authors' contributions

Rui He: Conceptualization, Methodology, Software. Teng Zeng and Rui He: Data curation, Writing- Original draft preparation. Rui He: Visualization, Investigation. Guangqiang Zhao: Supervision. Chao Ming and Yuan Ma: Software, Validation. Rui He: Writing- Reviewing and Editing. Yunchao Huang: Project administration. Guangjian Li: Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the Ethics Review Committee of the Third Affiliated Hospital of Kunming Medical University (No.SLKYLX2023-212), which waived the requirement for informed consent as it was a retrospective study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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