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Original Article

Evaluation of the Possible Risk Factors on Bronchial Closure Techniques for Bronchopleural Fistula after Lung Resection

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Abstract

Background: Broncho-pleural fistula (BPF) can occur after pulmonary resections as a complication with high morbidity and mortality rates.

Aim: In the present study, we analyzed the relation between the possible risk factors and the two major bronchial closure techniques for BPF after lung resections, and the management methods of BPF.

Materials and methods: A total of 26 cases detected and managed with BPF diagnosis in our clinic between September 2005 and September 2017 were evaluated retrospectively. The cases were divided into two groups: Group 1 (n=14); bronchial closure performed manually and Group 2 (n=12) bronchial closure with stapler. We analyzed cases for age, gender, body mass index, pulmonary function tests, time to fistula, total protein/albumin level, length of hospital stay, bronchial stump distance, presence of bronchial stump coverage, and the mean survivals.

Results: Twenty-three of the cases were males (88.5%) with a mean age of 60.03±8.7 years (range 38-73). While BPF was detected in twenty-three (88.5%) of the cases after pneumonectomy, three (11.5%) of them were after lobectomy. There was no statistically significant correlation between the two groups in gender, age, BMI, preoperative FEV1, time to fistula, total protein/albumin level, length of hospital stay, bronchial stump distance, and presence of bronchial stump coverage (chi-square test, $p>0.05$). As a result of the applied Kaplan-Meier analysis, we found no statistically significant difference in the mean survival rates between the two groups ($p>0.05$).

Conclusions: Broncho-pleural fistulas still remains a major challenge. Although there is no statistical relationship between bronchial closure techniques and possible risk factors in our study, patients should be assessed in terms of possible risk factors. The management strategy for BPF varies according to individual patients' clinical condition, the size of the fistula, and development time.

Keywords

bronchus, fistula, thorax, surgery

BACKGROUND

Broncho-pleural fistula (BPF) is called a communication between the bronchial system and the pleural space. It can be seen after pulmonary resections. BPF is one of the most important and difficult complications of thoracic surgery operations with high morbidity and mortality rates.[1] The incidence increases with underlying infectious diseases such as tuberculosis and empyema.[2] Diagnosis and localisation of BPF is sometimes challenge and can require some advanced imaging methods. It is universally accepted that

the "gold standard" for the diagnosis of BPF is bronchoscopy. Successful management of a fistula is difficult and the treatment is sophisticated if accompanied with empyema.[3]

AIM

The aim of this study is to analyze the possible risk factors of BPF and management methods. For this purpose, we compared the two techniques which were used in bronchial closure (manual and stapler) in our study.

MATERIALS AND METHODS

A total of 26 cases with BPF who underwent anatomic lung resection (lobectomy-pneumonectomy) in our clinic between September 2005 and September 2017 were included in the study. Twenty-three of the cases were males (88.5%) and three (11.5%) were females with a mean age of 60.03±8.7 years (range 38-73). Case registry was analyzed retrospectively. Twenty-one patients were operated in our clinic while the five patients were in other surgical centers. BPFs were seen in 23 patients (88%) after pneumonectomy and in three (3%) patients after lobectomy.

BPFs were found in eighteen patients (10.3%) of 174 patients who underwent pneumonectomies during the 12-years period in our clinic. Also, BPF rate was 0.8 % with three patients of lobectomy applied in 356 patients. The other five patients who were operated at the external center and were diagnosed and managed for BPF in our clinic were included in the study.

Nonanatomic lung resections (wedge resection), segmentectomies and bronchoplastic sleeve resections were excluded from the study.

By reviewing the medical and surgical records from patient files, demographic features, treatment strategies, surgical outcomes-techniques, possible causes of fistula, clinical features, and BPF management were reviewed. In all cases detailed medical histories were taken. Symptoms such as dyspnea, high fever, subcutaneous emphysema, coughing and sputum present were questioned. All patients were evaluated using chest X-ray, thorax CT, and fiberoptic bronchoscopy to confirm the fistula. As first step treatment, tube thoracostomy was performed with empirical antibiotics until getting the microbiological culture results of pleural effusion.

Early BPFs were observed within a month after pulmonary resection in nine patients (35%) and late BPFs were observed after one month in 17 patients (65%). Endoscopic and operative techniques for closing the fistula in early stage cases were tried. In the late period, because the BPF becomes complicated, the struggle with infections and the adequate drainage to protect the other lung tissue became the priority.

Factors affecting the incidence of BPF after anatomic resections (lobectomy-pneumonectomy) were analyzed. Two main techniques were used for bronchial closure. TA 30-4.8 mm bronchus staples were used in stapler technique. In patients with manual closure, 2/0 monofilament polypropylene was used separately.

Patients were divided into two groups according to bronchial closure technique: Group 1 (n=14); bronchial closure with manually, and group 2 (n=12) bronchial closure with stapler. In the study design, albumin and total protein values were measured in the preoperative 1-7-day period and bronchial stump distance was measured in the coronal section of postoperative chest CT. Total protein normal range was accepted as 6.5-8.5 gram/d L and albumin normal range as 3.5-5.5 g/dL.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science program (SPSS, 20.0). Data were expressed as mean ±SD. Frequencies and percentages were used for the categorical variables. In the evaluation of the data, descriptive statistical methods (mean, standard deviation) as well as repetitive variance analysis in repeated measures of groups, independent *t* test in comparison of two groups and chi-square test in comparison of qualitative data were used. Kaplan-Meier test was used for survival analysis. P-values <0.05 were considered statistically significant.

RESULTS

Broncho-pleural fistula was detected in 23 (88%) cases of the male patients, 3 (12%) of the female patients; 25 (96%) were over 40 years old and one (3.8%) was under 40 years old. BPF was observed after right pneumonectomy in 17 (65%) of them, after left pneumonectomy in six (23%) of them, after right upper lobectomy in two (8%) of them and after inferior bilobectomy in one (4%) of them. Body Mass Index (BMI) was less than 20 in 18 (69%) patients, and preoperative FEV1 was less than 2 litres in 7 (27%) patients. BPF was seen in 9 (35%) cases before one month, in three (12%) cases between one month and one year, and in 14 (53%) cases after one year. Total protein-albumin values were lower in 19 (73%) patients. Bronchial stump distance was measured to be longer than 15 mm in 8 (31%) cases.

BPFs were developed in 12 (46%) patients despite the bronchial stump reinforcement (parietal pleura in 7, pericardial fatty tissue in 5 patients).

Seven (27%) of the cases had been post-obstructive pneumonia in preoperative period. BPF had developed although antibiotics were applied preoperatively in these cases.

In two cases of BPF after lobectomy, endobronchial cauterization was performed due to hemoptysis in the preoperative period by the chest physicians. We consider that this approach may have led to BPF by impairing bronchial circulation. While 19 (73%) of the pulmonary resection in-

dications were lung cancer (squamous cell carcinoma in 17, adenocarcinoma in 2 patients), seven (27%) of them were non-oncological causes (tuberculosis in 3, bronchiectasis in 2, hydatid cyst in 2 patients).

All cases operated for lung cancer were in II B or lower stages. Five of these cases had received neoadjuvant chemotherapy and seven – adjuvant chemotherapy. None of them had radiotherapy. Bronchial surgical margin positivity was detected in any patient.

In 17 (65%) of the cases, comorbidities were determined (type 2 diabetes mellitus in seven, hypertension in six, malignancy in four, coronary artery disease in two, rheumatoid arthritis in one, polio sequelae in one and drug addiction in one). Mechanical ventilation was required in four (15%) of the cases during the early postoperative period (1-3 days) **(Table 1)**.

Fistulas smaller than 5 mm were closed via bronchoscopy with fibrin tissue adhesives in three patients who had an early BPF with failure. All nine patients with early BPF underwent rethoracotomy. Bronchial stump was debrided and bronchial stump reinforcement was performed using intercostal muscle in four of them, latissimus dorsi muscle flap in two of them, pericardial fatty tissue in two of them, and diaphragm in one patient. Fistula closure was successful in five of nine patients (early period success rate, 55%) with early rethoracotomy. Also, the bronchial stump was debrided, reclosed manually in three of patients with late BPF. The stump was covered with intercostal muscle flap in two of them, and pericardial fatty tissue in one. Fistula closure was successful only in one of these three patients (late period success rate 33%) **(Fig. 1)**.

The surgical closure was successful in a total of 6 (50%) of 12 rethoracotomy applied patients (early period in 5 (55%), late period in one (33%). Continuous drainage methods

Table 1. Evaluation of preoperative and postoperative outcomes and possible risk factors of 26 patients

No	Operation	Indication	Stage	Neoadjuvant therapy	Adjuvant therapy	Comorbidity	Postoperative mechanical ventilation
1	RP	SqCLC	IIA	√	Ø	Drugs & alcohol addiction	Ø
2	RP	SqCLC	IIB	√	√	HT	Ø
3*	LP	Hydatid cyst	-	Ø	Ø	DM, CAD	Ø
4	LP	SqCLC	IIA	Ø	Ø	HT	Ø
5	IBL	SqCLC	IA	Ø	Ø	DM	√
6	RUL	Tuberculosis	-	Ø	Ø	DM, polio-sequel	Ø
7	LP	SqCLC	IIB	Ø	√	Ø	Ø
8	RP	SqCLC	IIA	Ø	Ø	RA, Prostate CA	√
9	RP	SqCLC	IIB	Ø	Ø	HT	√
10	RP	AC	IIB	√	√	Bladder CA	Ø
11	RP	SqCLC	IIA	Ø	√	HT, CAD	Ø
12	RP	SqCLC	IIA	Ø	Ø	Renal Cell CA	Ø
13	RP	SqCLC	IIA	Ø	√	DM	Ø
14	RP	SqCLC	IIA	Ø	√	Larynx CA	Ø
15*	LP	Tuberculosis	-	Ø	Ø	DM, HT	Ø
16*	RP	Hydatid cyst	-	Ø	Ø	DM	Ø
17	LP	SqCLC	IIB	√	√	Ø	Ø
18	RP	Bronchiectasis	-	Ø	Ø	Ø	Ø
19*	RP	Tuberculosis	-	Ø	Ø	Ø	Ø
20	RP	SqCLC	IIA	Ø	Ø	Ø	Ø
21	RP	SqCLC	IIA	Ø	Ø	Ø	Ø
22	RUL	Bronchiectasis	-	Ø	Ø	Ø	Ø
23	LP	AC	IIA	Ø	Ø	HT	Ø
24	RP	SqCLC	IIA	Ø	Ø	Ø	√
25*	RP	SqCLC	IIA	Ø	Ø	Ø	Ø
26	RP	SqCLC	IIA	√	Ø	DM	Ø

* Patients with bronchopleural fistulas who underwent pneumonectomy at external centers and were treated and managed at our clinic.

RP: right pneumonectomy, LP: left pneumonectomy, RUL: right upper lobectomy, IBL: inferior bilobectomy, SqCLC: squamous cell lung cancer, HT: essential hypertension, DM: diabetes mellitus, CAD: coronary artery disease, RA: rheumatoid arthritis, CA: carcinoma

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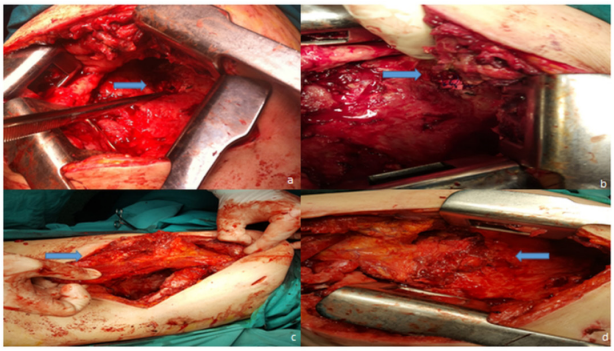

Figure 1. a) Intraoperative view of bronchopleural fistula after right pneumonectomy; b) After fistula repaired with pledgeted sutures; c) Preparation of transposed pedicled serratus anterior muscles flap; d) Support of bronchial stump repaired by serratus anterior muscle flap.

such as Elooser flap (in 13 cases) – permanent Pezzer drain (in three cases) was needed in 16 patients.

Bronchial re-inforcement methods, fistula closure success rate, microbiological culture results and survival were summarized in **Table 2**.

Two groups were evaluated statistically according to factors possibly affecting the BPF. There was no statistically significant correlation between the two groups and gender, age, BMI, preoperative FEV1, time to fistula, total protein/albumin, length of hospital stay, bronchial stump distance and bronchial stump coverage as a result of univariate analysis (chi-square test, $p>0.05$) **(Table 3)**.

There was no statistically significant difference in the mean survival between the two groups ($p>0.05$) in Kaplan-Meier analysis. At a mean follow-up time of 51.4

Table 2. Treatments performed after BPF, microbiological culture results and survival times of 26 cases

No	Treatments performed after BPF	Bronchial strengthening method after rethoracotomy	Success after rethoracotomy	Culture of sputum-pleural fluid	Survival
1	TT+ Eloesser flap	Ø	-	Ø	42 months, alive
2	TT, FOB+FG, RT, Eloesser flap	Intercostal muscle flap	Ø	PA,CA	73 months, alive
3*	TT, VAC, Eloesser flap	Ø	-	EC	144 months, exitus
4	TT, RT	Pericardial fat tissue	√	Ø	68 months, alive
5	TT, RT, PPD	Pericardial fat tissue	Ø	PA	14 months, alive
6	TT, RT	Latissimus dorsi muscle flap	√	Ø	12 months, alive
7	TT, PPD, Tracheal stent	Ø	-	Ø	25 months, exitus
8	TT, Eloesser flap	Ø	-	Ø	122 months, alive
9	TT, Eloesser flap	Ø	-	SM	38 months, exitus
10	TT, CP, RT, Eloesser flap	Intercostal muscle flap	Ø	Ø	42 months, exitus
11	TT, CP, FOB+FG, RT	Intercostal muscle flap	√	Ø	18 months, exitus
12	TT, CP, Eloesser flap	Ø	-	Ø	23 months, exitus
13	TT, RT, Eloesser flap	Intercostal muscle flap	Ø	Ø	42 months, exitus
14	TT, CP, PPD	Ø	-	Ø	2 months, exitus
15*	TT, Eloesser flap	Ø	-	PA	161 months, exitus
16*	TT, Eloesser flap	Ø	-	EC	600 months, alive
17	TT, CP	Ø	-	PA	5 months, exitus
18	TT, RT	Diaphragm flap	√	Ø	96 months, alive
19*	TT, Eloesser flap	Ø	-	Ø	396 months, alive
20	TT, RT, PPD	Latissimus dorsi muscle flap	Ø	CA	40 months, alive
21	TT, CP	Ø	-	Ø	96 months, alive
22	TT, FOB+FG, RT	Intercostal muscle flap	√	Ø	116 months, alive
23	TT, RT, Eloesser flap	Intercostal muscle flap	Ø	Ø	98 months, exitus
24	TT, RT	Pericardial fat tissue	√	Ø	88 months, alive
25*	TT, Eloesser flap	Ø	-	Ø	68 months, exitus
26	TT, PPD	Ø	-	Ø	114 months, alive

* Patients with bronchopleural fistulas who underwent pneumonectomy at external centers and were treated and managed at our clinic.

TT: tube thoracostomy, FOB: fiberoptic bronchoscopy, FG: fibrin glue, RT: rethoracotomy, VAC: vacuum assisted closure, PPD: permanent Pezzer drain, CP: Clagett procedure, PA: *Pseudomonas aeruginosa*, CA: *Candida albicans*, EC: *Escherichia coli*, SM: *Serratia Marcescens*

Table 3. Statistical analysis of possible fistula evaluation mechanisms between Group 1 (bronchial closure performed manually) and Group 2 (bronchial closure with stapler)

Variable	Group 1 (with manually) (n=14)	Group 2 (with stapler) (n=12)	p value
Gender (M/F)	12/2	11/1	1.000
Age <40 years >40 years	 14 0	 11 1	 0.462
BMI <20 >20	 9 5	 9 3	 1.000
*Preoperative FEV1 <2 lt >2 lt	 4 6	 3 8	 1.000
Time to fistula <1 month >1 month	 5 9	 4 8	 1.000
*Total protein / Albumin Normal Abnormal	 0 10	 2 9	 0.476
#*Length of hospital stay <10 days >10 days	 3 7	 3 8	 1.000
Bronchial stump distance <15 mm >15 mm	 11 3	 7 5	 0.401
Presence of bronchial stump coverage Yes No	 6 8	 6 6	 0.716
Presence of post-obstructive pneumonia	4	3	Statistically non-significant

after first operation, * these values are only for 21 patients who had been operated on in our clinic.

BMI: body mass index, Total protein normal value is 6.5-8.5 gram/dL, Albumin normal value is 3.5-5.5 g/dL,

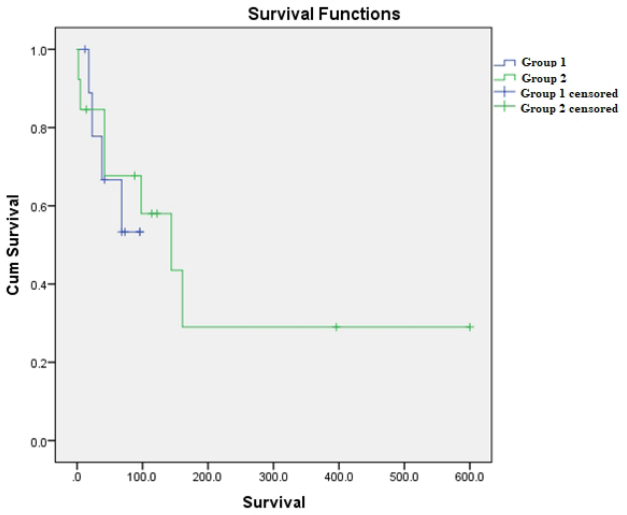

Figure 2. Group 1 (bronchial closure performed manually) and Group 2 (bronchial closure with stapler) survival analysis.

months (range 10-110 months), the overall survival was 97.8 months. Median survival was 69.04 months in group 1 and 105.4 months in group 2 (**Table 4, Fig. 2**).

Twelve patients died during the follow-up period: tumor progression in four, empyema-pneumonia-sepsis in four, acute renal failure in three, cardiac failure in one. But only in five patients (19%) death causes were associated with BPF

Morbidity was 14 of 26 cases (54%). Causes of morbidity were empyema-pneumonia-sepsis (n=8), acute renal failure associated with intensive antibiotic use (n=3), atrial fibrillation (n=2) and pulmonary edema (n=1). Empyema-pneumonia-sepsis cases were treated with drainage and sensitive systemic antibiotherapy. Acute renal failures were treated with hemodialysis. For cases with atrial fibrillation, antiarrhythmic and anticoagulation treatments were used. Pulmonary edema declined within days after oxygen inhalation, bronchodilator and diuretic treatments.

DISCUSSION

Lung resection cases have increased in recent years. Although resection rates for bronchiectasis, tuberculosis, lung abscess and fungal infections decrease, surgical resec-

Table 4. Survival analysis of the two groups.

Variable	N	Mean (months)	95% Confidence interval		Chi-square	*p* value
			Lower bound	Upper bound		
Group 1 (closure performed manually)	14	69.04	28.010	80.079		
Group 2 (closure with stapler)	12	105.4	66.403	174.458	0.219	0.640
Overall	26	97.8	64.267	160.990		

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tion for lung cancer has increased in recent years. One of the important steps in the surgical procedure of lung resections is the closure of the bronchus, which provides air inflow to the lung tissue. The bronchial closure techniques are one of the most important factors affecting morbidity and mortality after operation.[4-7] BPF is a connection between the tracheobronchial tree and the pleural space leading empyema. BPF is the most feared complication after thoracic surgery. The incidence of BPF varies from 4.5% to 20% after pneumonectomy and is only 0.5% after lobectomy.[6] Mortality rate is as high as 20%-70%.[7]

After pneumonectomy BPF has been associated with respiratory failure, subcutaneous emphysema, mediastinal and tracheal shift on non-pathological side. In patients with BPF after lobectomy, prolonged air leakage, purulent drainage, cough, fever, empyema, and air-fluid level in the thorax and cavitation in the chest x-ray can be detected. Fiberoptic bronchoscopy can be used in the diagnosis and management of BPF. Closure of BPF by interventional bronchoscopy using sealants, tracheal stents, endobronchial devices, sclerotherapy can be possible down to 5-8 mm.[4-7]

The first line treatment method should be drainage, appropriate antibiotherapy and supportive care. The primary goal is to prevent sepsis and protect the contralateral lung. Other therapeutic alternatives must be decided according to whether BPF is in early or late period.[8-10] The most effective and valid method in early BPF is re-suturing the bronchus with surgical intervention. In late-stage and large fistulas open-window thoracostomy (Elooser flap) appears to be a good alternative treatment.[11] Autologous tissues such as omentum, muscle, pericardial or pleural flaps can be used in re-operated cases for bronchial reinforcement and vascularisation. Thoracoplasty can be added this procedure.[12] Some authors reported different closure methods such as atrial septal occluder device or Amplatzer device that could be used successfully to close BPF.[13,14] Bobocea et al.[15] reported that videomediastinoscopic transcervical approach could be used successfully for BPF in selective cases. We think that the most accurate management for BPF is the individualization according to patients' general condition (sepsis, performance status, survey etc.) and fistula size.

A lot of risk factors affecting the BPF have been researched in the literature. These factors can be divided into two groups as factors belonging to the patient and the operation technique. The first group includes age (increased risk of advanced age), gender (common in males), general condition, lung infections (especially tuberculosis and fungal infections), preoperative or postoperative chemotherapy and radiotherapy, residue tumor remain, diabetes mellitus, postoperative respiratory insufficiency requiring ventilatory support, material used in bronchial closure, preoperative or postoperative infections, postoperative haemorrhages, impairment of the bronchial vascularization in preoperative period. The second group includes long bronchial stump distance, unsuitable suture material, sutures are too tight and stretched, extreme skeletonization of the bronchus, bronchial artery grafting or cauterization, inadequate closure of the bronchial instillation, and bleeding to the thoracic cavity.[16,17] In our study, possible risk factors were assessed with bronchial closure methods and no statistical difference was found between the two groups. However, we found that 88% of the cases were male, 96% were over 40 years, 69% of the patients had a BMI below 20, 65% of patients had a comorbidity, and in 73% of them the total protein/albumin values were abnormal, preoperatively endobronchial cauterisation (n=2) as a possible risk factor.

It has also been reported in the literature that fistulas may be spontaneously closed. Hollaus et al.[18] evaluated 96 patients with bronchopleural fistula after pneumonectomy. They found that in 11% of the patients, BPF was closed by performing only tube thoracostomy, and in one patient BPF was closed conservatively. In our study, there was no BPF that closed with tube thoracostomy or spontaneously.

Yazgan et al.[19] reported of 50 patients with BPF whose five-year survival was 39%. The total BPF rate in their study was 3.2%, the mean follow-up was 40.9 months (range 0-121 months). In our study, the overall survival was 97.8 months at a mean follow-up time of 51.4 months (range 10-110 months), Overall mortality and BPF-related mortality rates were 46% and 19%, respectively

STUDY LIMITATIONS

We acknowledge some limitations in our study. First, the most important is the retrospective study design, similar to most of the studies in the literature. Secondly, our findings are obtained from a single institution and from a small number of case samples. Therefore, the findings cannot be generalised to all BPF patients. Despite these limitations, the current study provides valuable information about the possible risk factors on the main two bronchial closure techniques of BPF after lung resection and the management methods of BPF.

CONCLUSIONS

Broncho-pleural fistula remains a major challenge. Although there is no statistical relationship between bronchial closure techniques and possible risk factors in our study, patients should be assessed in terms of possible risk factors. In the treatment of BPF, the first goal is to prevent sepsis and contamination of the healthy lungs. Surgical repair of BPF may be considered in patients after adequate pleural drainage by suture closure and reinforcement of bronchial stump with vascularized pedicle flaps. During the preoperative period and resection time, disruption of bronchial vascularization should be avoided. Successful management of postresection BPF needs aggressive control of infection, and individualized approach to each patient.

Acknowledgments

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Оценка вероятных факторов риска при методах закрытия бронхолёгочного свища после резекции лёгкого

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Абстракт

Введение: Бронхоплевральный свищ (БПС) может возникать после лёгочной резекции как осложнение с высоким уровнем заболеваемости и смертности.

Цель: В этом исследовании мы проанализировали взаимосвязь между вероятными факторами риска и двумя основными методами закрытия бронхов при БПС после резекции лёгких и методами контроля БПС.

Материалы и методы: В общей сложности 26 случаев, выявленных и пролеченных в нашей клинике в период с сентября 2005 года по сентябрь 2016 года, были оценены ретроспективно. Случаи были разделены на две группы: группа 1 (n = 14) (закрытие бронхов выполнялось вручную) и группа 2 (n = 12) (закрытие бронхов с помощью степлера). Мы проанализировали случаи на предмет возраста, пола, индекса массы тела, теста функции лёгких, времени для развития свища, уровня общего белка / альбумина, продолжительности пребывания в стационаре, расстояния от бронхиальноой культи, наличия покрытия бронхиальной культи и средней выживаемости.

Результаты: 23 случая были у мужчин (88,5%) со средним возрастом 60,03 ± 8,7 года (диапазон 38-73 года). В то время как БПС был обнаружено в 23 (88,5%) случаях после пневмонэктомии, три (11,5%) из них были после лобэктомии. Не было статистически значимой корреляции между двумя группами с точки зрения пола, возраста, ИМТ, предоперационного ОФВ1, времени развития свища, уровня общего белка / альбумина, продолжительности пребывания в стационаре, расстояния от бронхиальной культи, наличия покрытия бронхиальной культи (Хи-квадрат тест, $p>0,05$). В результате примененного анализа Kaplan-Meier мы не обнаружили статистически значимой разницы в средней выживаемости между двумя группами ($p> 0,05$).

Вывод: Бронхоплевральные свищи всё ещё представляют собой серьёзную проблему. Хотя в нашем исследовании нет статистически значимой связи между методами закрытия бронхов и вероятными факторами риска, пациенты должны быть оценены на предмет возможных факторов риска. Стратегия борьбы с БПС варьируется в зависимости от индивидуального состояния пациента, размера свища и времени развития.

Ключевые слова

грудная клетка, хирургия, бронх, свищ