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Analysis of recurrence of risk factors after transcatheter bronchial artery embolization for hemoptysis

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BACKGROUND: As a proven and preferred technique for hemoptysis, bronchial artery embolization (BAE) cannot avoid the possibility of postoperative recurrence; however, few studies have examined the causes of hemoptysis recurrence after BAE.

OBJECTIVES: Identify the risk factors for hemoptysis recurrence after BAE treatment.

DESIGN: Retrospective

SETTING: Tertiary training and research hospital

PATIENTS AND METHODS: A retrospective analysis was conducted on 406 patients with hemoptysis, 55 patients who developed with recurrent postembolization hemoptysis, covering the period from January 2011 to January 2021. Single factor analysis and multiple factor logistic regression were used to analyze high-risk factors for hemoptysis recurrence.

MAIN OUTCOME MEASURES: The incidence and risk factors for recurrence hemoptysis associated with transcatheter BAE.

SAMPLE SIZE: 406 patients

RESULTS: Multivariate logistic regression analysis showed that preoperative computed tomography angiography (CTA) (odds ratio [OR]: 0.052, 95% CI: 0.012–0.225), tumor-related hemoptysis (OR: 20.753, 95% CI: 6.778–63.545), pleural thickening (OR: 3.168, 95% CI: 1.081–9.286), and bilateral lung lesions (OR: 8.442, 95% CI: 2.449–29.101) had a statistically significant impact on the recurrence of hemoptysis after BAE.

CONCLUSIONS: Preoperative CTA serves as a protective factor against hemoptysis recurrence, whereas tumor-related hemoptysis, pleural thickening, and bilateral lung diseases are significant risk factors for hemoptysis recurrence following interventional therapy.

LIMITATIONS: This was a retrospective analysis of a single center with a small sample, which may have a certain degree of recall bias when collecting data, thus, reducing the reliability of the results.

CONFLICT OF INTEREST: None.

Hemoptysis is a common emergency in clinical practice; massive hemoptysis is defined as a hemoptysis volume exceeding 100 mL in one episode or more than 500 mL within 24 h. The curative effect of conservative medical treatment is poor, and the mortality of traditional surgical resection treatment is high, with an overall mortality rate as high as 50–75%.[1,2] Therefore, it is a serious life-threatening disease. Transcatheter bronchial artery embolization (BAE) was first reported in 1974.[3] It is favored by clinicians because it is a safe, minimally invasive, and a repeatable technique for the treatment of hemoptysis, which has good short- and long-term effects.[3] Therefore, BAE has become a proven and preferred technology for the treatment of massive hemoptysis at present, with the success rate of immediate hemostasis reaching 91.9–94%.[4,5] It is widely accepted and adopted in clinics due to its definite hemostatic effect, but it is reported that 5-10% of patients still fail or relapse within a short time after the first treatment,[6] mainly due to arterial omission.[7] The follow-up results showed that the long-term recurrence rate of patients fluctuated between 10-43.2%.[8,9] Vascular recanalization and reconstruction and primary disease progression after embolization are the main causes of these recurrent events.[10,11] Approximately 40-60% of patients with recurrent hemoptysis must undergo secondary embolism, lobectomy or death.[12]

Although initial treatment with BAE can be successful, the risk of hemoptysis recurrence remains. However, there is limited research on the factors contributing to recurrence, and addressing how to lower the recurrence rate by mitigating these risk factors is an urgent issue that needs to be resolved. In this study, regression analysis was conducted on the risk factors for hemoptysis recurrence after BAE treatment. The study aimed to identify the risk factors for hemoptysis recurrence after BAE and determine active prevention and control measures to reduce the occurrence and risk of hemoptysis.

PATIENTS AND METHODS

This retrospective analysis was performed on patients with hemoptysis who visited our department between January 2011 and January 2021. All patients signed an informed consent form for interventional treatment before the operation, and this study was approved by the Ethics Committee. The inclusion criteria were as follows: patients with massive hemoptysis (hemoptysis volume >100 mL in one episode or hemoptysis volume >500 mL within 24 hours) or patients with repeated hemoptysis and ineffective conservative medical treatment who received BAE for the first time. The exclusion criteria were as follows: patients who previously underwent BAE, those who had failed interventional embolization, and those who died or were lost to follow-up after BAE. Hemoptysis caused by active pulmonary tuberculosis and pulmonary aspergillosis patients was not included in this study.

The recurrence of hemoptysis was defined as hemoptysis volume of 100 mL in one episode or 500 mL within 24 hours after embolotherapy, which required and underwent a repeat BAE treatment.

BAE procedure

The procedure was carried out by using a 5-Fr introducer sheath from Terumo, Japan. Access to the common femoral artery was achieved via the Seldinger technique. 5-Fr curved catheters such as Cobra, Mik, or Simmons were utilized. Coaxial microcatheters (Carnelian 2.6-Fr; Asahi, Japan) were guided by the 0.014-inch M guidewire also from Asahi (Japan). For all arteries that show tortuous enlargement of bronchial arteries and/or non-bronchial systemic arteries in the lesion area, or those with branch vessels entering the pulmonary vessels, embolization was performed. The embolic agents comprise a combination of polyvinyl alcohol (PVA; size range, 350–710 μm; Boston Scientific, USA) and/or embolization coils (3/2 mm and/or 4/2 mm; Cook Medical, US). Whether it was the first or second BAE, the process was the same. BAE was conducted by two interventional radiologists, both of whom had more than ten years of experience in vascular intervention. The interventional process is shown in **Figure 1**.

Based on the admission case records, outpatient follow-up consult, and telephone follow-ups, the following data were gathered: age and sex composition, body mass index (BMI), basic chronic diseases (hypertension, diabetes), smoking history, use of anticoagulant or antiplatelet drugs, recurrence and time of hemoptysis, causes of hemoptysis, hemoptysis volume, imaging characteristics of hemoptysis lesions, use of computed tomography angiography (CTA) before BAE, types of embolic substances, and other data were collected.

Under age composition, old age was defined as older than 65 years old. Body mass index (BMI) was categorized as overweight if the computed value was above 24. Smoking history was determined if the patient was smoking every day for more than one year immediately before the procedure. Anticoagulant or antiplatelet drug intake was defined as use of anticoagulant or antiplatelet drugs for more than six months. Hemoptysis based on etiology was categorized into

neoplastic hemoptysis (induced by a malignant tumor) or non-neoplastic hemoptysis (caused by bronchiectasis, pulmonary tuberculosis, arteriovenous malformations, etc.). The imaging characteristics of hemoptysis were as follows: bilateral lesions (in both left and right lungs), or unilateral lesions (if the lesions involved only one lung). Pleural thickening was defined as pleural hypertrophy. The types of embolic materials were divided into polyvinyl alcohol (PVA) alone and PVA combined with embolization coil.

Statistical analysis

IBM SPSS software (version 23.0) was used for the analysis. In the first step, a single variable analysis was used to analyze data and χ^2 test was used to compare and screen risk factors. The second step was to analyze the influence of various risk factors on hemoptysis recurrence using a multivariate logistic stepwise regression method. The odds ratio (OR) was used to evaluate the factors affecting the recurrence of hemoptysis. The Kaplan–Meier test was used to analyze and compare the recurrence rate of hemoptysis between the two groups who received BAE for the first time and those who needed another embolization due to recurrence after initial intervention therapy. The continuous variable age is expressed as median and IQR since it did not follow a normal distribution. Statistical significance was set at $P<.05$.

RESULTS

The 406 patients included 319 male patients and 87 female patients, with a median (IQR) age of 64.57 (12.89) (38–83 years old). There were 55 patients (13.55%) who experienced recurrence of hemoptysis) (**Table 1**). The average follow-up time was 24.8 months (1–61 months).

The results of the univariate analysis showed that the risk factors for hemoptysis recurrence were tumor-related hemoptysis, pleural thickening on imaging, and bilateral lung involvement (**Table 2**). The recurrence rate of tumor-related hemoptysis (52.63%) was significantly higher than that of non-tumor related hemoptysis (4.55%). The recurrence rate of hemoptysis in patients with pleural thickening (44.93%) was significantly higher than that in patients without pleural thickening (7.12%). The recurrence rate of hemoptysis in patients with bilateral lung diseases (38.98%) was significantly higher than that of patients with unilateral lesions (3.13%). However, the recurrence rate of hemoptysis in patients with PVA + embolization coil and preoperative bronchial artery CTA examination was significantly lower than that in patients with PVA alone or without preoperative CTA examination. Other factors, including age, sex composition, BMI, basic diseases, and smoking history, had little influence on the recurrence of hemoptysis.

Multivariate logistic regression analysis showed that preoperative CTA was a protective factor controlling for hemoptysis recurrence (**Figure 2**). The incidence of postoperative hemoptysis was only 0.052 times higher than that in patients without CTA. However, the type of embolic material had a relatively lower impact on hemoptysis recurrence, and the difference was not statistically significant. Tumor-related hemoptysis, pleural thickening, and bilateral lung diseases were statistically significant high-risk factors for recurrence of hemoptysis. Tumor hemoptysis was the most dangerous factor for the recurrence of postoperative hemoptysis, with 20.753 times that of patients with non-tumor hemoptysis.

The results showed that the recurrence time of tumor-related hemoptysis after interventional therapy was significantly shorter than that of non-tumor hemoptysis [6.275 Â (2.602) versus 19.467 Â (5.939), t=11.52, $P<.0001$] (**Figure 3**). The results showed that the recurrence of hemoptysis in patients with pleural hypertrophy after intervention was significantly earlier

Table 1. Clinical characteristics of patients (n=406).

Parameter	
Age (years)	
≥65	242 (59.61)
<65	164 (40.39)
Sex	
Male	319 (78.57)
Female	87 (21.43)
BMI	
<24 kg/m^2	277 (68.23)
≥24kg/m^2	129 (31.77)
Hypertension	
Yes	177 (43.60)
No	229 (56.40)
Diabetes	
Yes	123 (30.30)
No	283 (69.70)
Recurrence of hemoptysis	
Yes	55 (13.55)
No	351 (86.45)

Table 2. Single factor analysis (The first term in each pair is the reference value).

Variable parameters	Number of recurrent hemoptysis (%)	OR	95% CI	χ^2	*P*
Age (years)		1.464	0.802–2.673	1.553	.213
≥65	37 (15.29)				
<65	18 (10.98)				
Sex		0.863	0.440–1.692	0.184	.668
Male	42 (13.17)				
Female	13 (14.94)				
BMI		0.951	0.518–1.744	1.274	.259
<24 kg/m^2	37 (13.36)				
≥24kg/m^2	18 (13.95)				
Hypertension		1.530	0.865–2.706	2.157	.142
Yes	29 (16.38)				
No	26 (11.35)				
Diabetes		1.253	0.687–2.287	0.544	.461
Yes	19 (15.45)				
No	36 (12.72)				
Smoking history		1.277	0.723–2.257	0.712	.399
Yes	27 (10.11)				
No	28 (16.23)				
Anticoagulants or antiplatelet drugs		1.337	0.679–2.631	0.709	.400
Yes	13 (16.46)				
No	42 (12.84)				
Causes of hemoptysis		23.333	11.747–46.349	121.962	**<.0001**
Neoplastic	40 (52.63)				
Non neoplastic	15 (4.55)				
Hemoptysis volume		1.155	0.616–2.166	0.202	.653
Massive hemoptysis	16 (14.81)				
Non massive hemoptysis	39 (13.09)				
Pleural lesion		10.639	5.664–19.983	69.896	**<.0001**
Thickening	31 (44.93)				
Not thick	24 (7.12)				
Range of lesion		19.806	9.263–42.346	91.898	**<.0001**
Both lungs	46 (38.98)				
One lung	9 (3.13)				
Embolic material		0.114	0.051–0.254	22.868	**<.0001**
PVA+coil	40 (10.90)				
PVA	15 (38.46)				
Preoperative CTA		0.199	0.107–0.371	29.590	**<.0001**
Yes	32 (9.44)				
No	23 (34.33)				

Data are number (percentage).

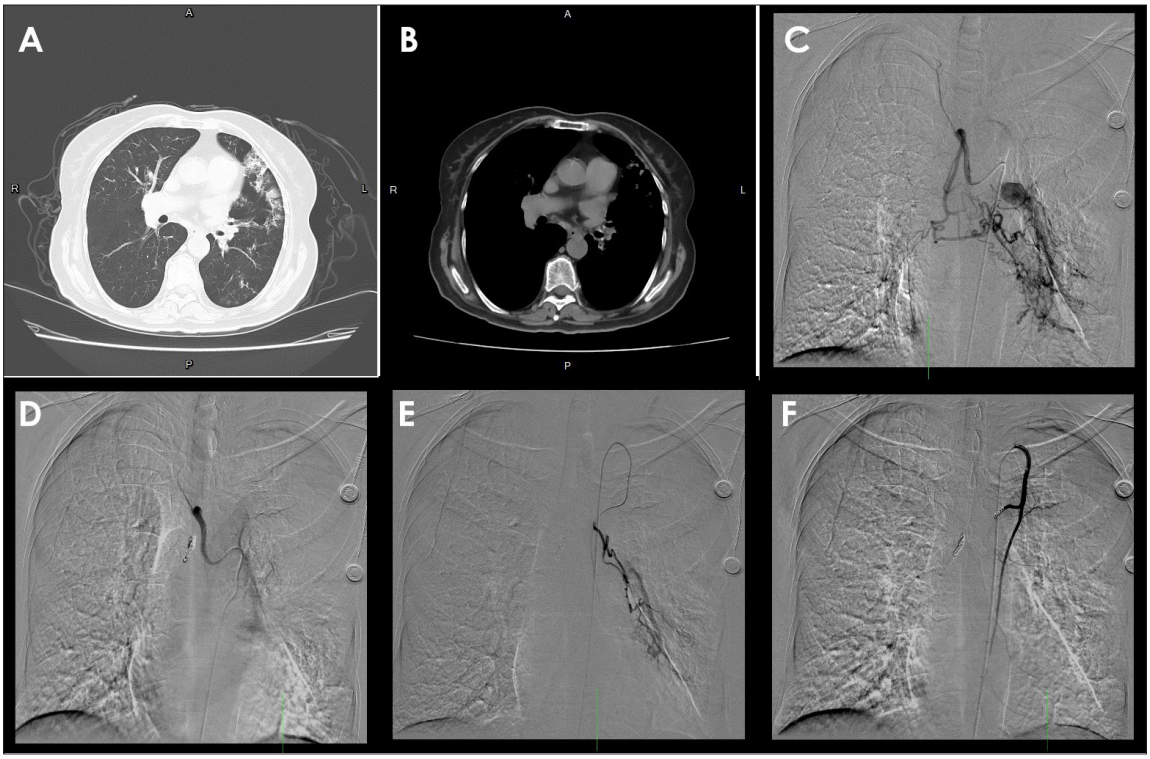

Figure 1. A 65-year -old female patient. A and B show the patient with left lung disease accompanied by hemoptysis. C and D show bronchial artery angiography and embolization process. The embolization material selected is PVA+coil. E and F show the involvement of the internal mammary artery branch in the blood supply of the lesion, and embolization is performed after angiography.

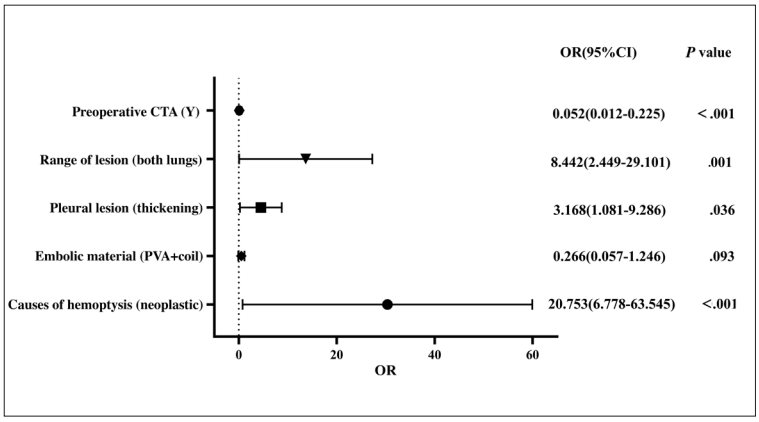

Figure 2. Ratio of risk factors by multiple logistic regression analysis.

than that in patients without pleural thickening [7.742 (4.711) versus 12.625 (8.515), t=2.707, *P*=.0091] (**Figure 4**). The results showed that the recurrence of hemoptysis in patients with bilateral lung disease after intervention was significantly earlier than that in patients with unilateral lung disease [8.739 (5.990) versus 15.667 (9.220), t=2.888, *P*=.0056] (**Figure 5**). The results showed that the recurrence time of hemoptysis in patients with preoperative CTA occurred significantly later than that in patients without preoperative CTA [13.964 Â (7.520) versus 4.857 Â (1.682), t=5.462, *P*<.0001] (**Figure 6**).

Figure 7 shows the Kaplan–Meier curve which illustrates the recurrence rate of hemoptysis after second BAE (3.63%), which was significantly lower than the 13.55% recurrence rate after the first BAE (χ^2=4.127, *P*=.042).

DISCUSSION

Primary diseases causing massive hemoptysis are bronchiectasis, pulmonary tuberculosis, tumor, etc. Bleeding often comes from bronchial arteries or systemic collaterals. With pneumonia/tumor, systemic circulation up, pulmonary down. Hemoptysis occurs when inflamed/tumor/necrotic tissue's vessels are damaged.[13] Diagnosing massive hemoptysis is easy but locating it is hard. Selective bronchial arteriography plays an important role in the qualitative and localized diagnosis of massive hemoptysis, and BAE can achieve immediate hemostatic effects.[3]

BAE shows satisfactory short-term efficacy in treating

massive hemoptysis. Previous literature indicates an immediate hemostasis rate of 75–92.8%.[3] However, some patients experience recurrence after BAE. Studies have shown mid- and long-term recurrence rates of 9.8–57.5% for massive hemoptysis treated with BAE.[14] The reasons for middle- and long-term recurrences after embolization include recanalization of the embolic artery after absorption of the embolic substance, opening or formation of collateral vessels, progression of the primary lesion, incomplete BAE, or change in the blood supply of the lesion. In this study, the recurrence rate of hemoptysis after interventional therapy was 13.55%. Since BAE has no effective medical control method for the primary lesion, the recurrence and progression of the lesion may be the main cause of hemoptysis recurrence. Currently, BAE is effective in most cases of hemoptysis. As the primary lesion remains uncontrolled or not surgically removed, there is a possibility of recurrence at any time. Thus, BAE can be a positive means to create conditions for surgical removal of pulmonary lesions. In cases of recurrence without surgical conditions, BAE can be performed again.

Univariate analysis identified tumor-related hemoptysis, imaging-detected pleural hypertrophy, and bilateral lung involvement as risk factors for hemoptysis recurrence. In contrast, the combination of PVA and coil embolization along with preoperative bronchial artery CTA examination acts as a protective factor against recurrence. Multivariate analysis results showed that the recurrence rate of tumor-related hemoptysis after BAE was 72.73% (40/55) of the total recurrences, much higher than non-tumor-related hemoptysis. The recurrence time for tumor-related hemoptysis after BAE was significantly shorter than non-tumor cases, being only 6.3 (2.6) months. Previous studies indicate that even with active treatment, tumor progression generally occurs within five to eight months.[15] This study found that the recurrence time of hemoptysis falls within this range. Additionally, other studies have shown that the recurrence time of hemoptysis in patients with tumor-related hemoptysis after intervention is 0.5–9.5 months,[16] consistent with this study. Some reports also suggest that the survival time of patients with tumor-related hemoptysis is significantly lower than those with non-tumor hemoptysis, with a median survival time of only 5.5 months,[17] indicating poor prognosis for tumor-related hemoptysis.

Regarding embolic agent type's influence on post-intervention hemoptysis recurrence, single-factor analysis showed PVA combined with embolization coil

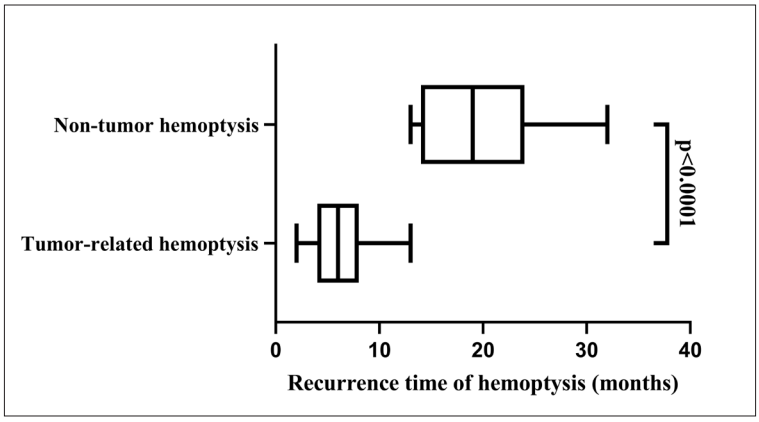

Figure 3. Comparison of recurrence time after interventional therapy for tumor and non tumor-related hemoptysis.

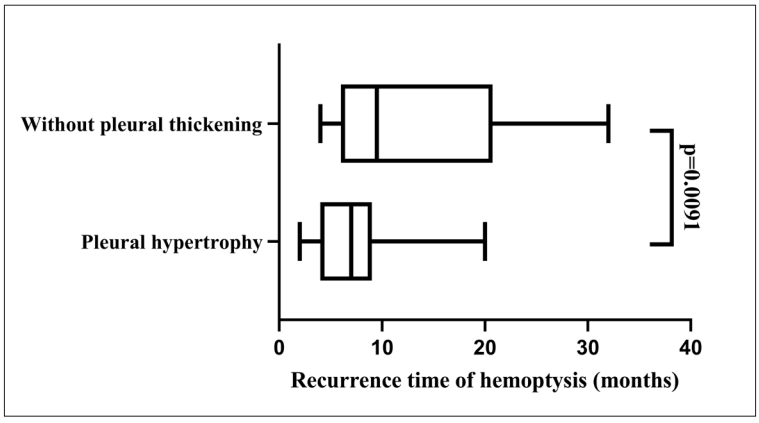

Figure 4. Comparison of the recurrence time after hemoptysis intervention with or without pleural thickening.

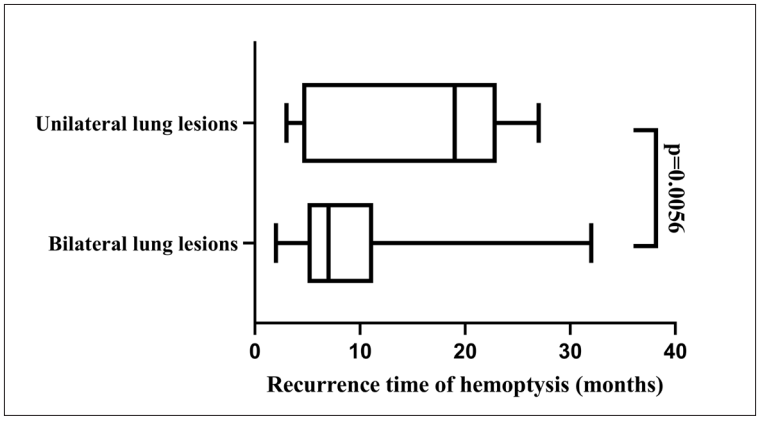

Figure 5. Comparison of recurrence time of hemoptysis caused by bilateral lung diseases after interventional therapy.

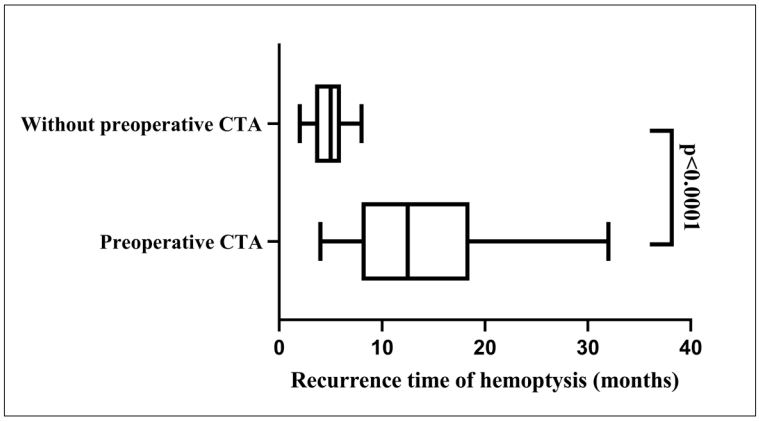

Figure 6. Comparison of recurrence time after hemoptysis intervention with or without CTA before operation.

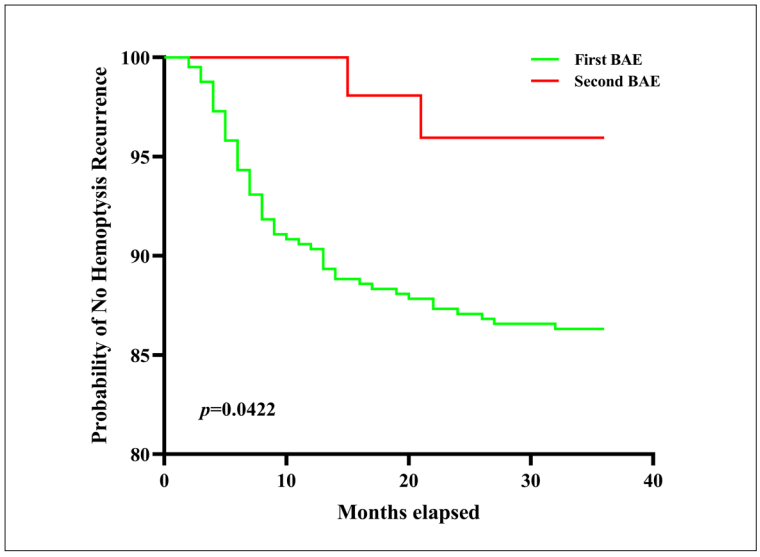

Figure 7. Kaplan -Meier analysis of hemoptysis recurrence between BAE group (*P*=.0422).

had a protective effect with statistical significance. But multifactor analysis differed. It indicated embolic agents had little influence and no significant difference. PVA and embolization coil are permanent agents. PVA mainly embolizes bronchial artery peripheral vessels, while the coil targets the trunk.[18,19] Both have good embolization performance. If PVA embolization is accurate, it may be possible to strengthen the embolization without using a coil. And it should be mentioned, that reinterventions can be impeded, if embolization coil is applied in the proximal part of bronchial arteries.[20]

Pleural thickening and bilateral lung diseases are risk factors for hemoptysis recurrence after BAE. The recurrence time for hemoptysis in these cases was 7.7 (4.7) and 8.7 (5.9) months. Previous studies have shown that patients with large hemoptysis, chest X-ray pleural thickening, and bilateral lesions who undergo BAE have an increased risk of recurrence.[21] When the pleura is involved, systemic circulation arteries outside the lung can enter the lung through thickened pleural adhesions, creating a complex blood supply network and shunts. This makes the lesions complex and prone to recurrence. Kwon et al reported that 230 pulmonary tuberculosis patients treated with embolism had poorer efficacy if they had pleural involvement. The more severe the pleural involvement, the greater the number of diseased blood supply vessels and the lower the hemostatic efficiency.[22] For bilateral lung disease, conservative medical treatment is generally ineffective. Due to lack of lung reserves, patients are often not suitable for surgery, so BAE is a more appropriate treatment.[23] Although the clinical success rate is still high, with disease progression, new blood vessels emerge, which is an important reason for hemoptysis recurrence. Thus, pleural thickening and bilateral lung disease are independent risk factors for hemoptysis recurrence after interventional operation.

Preoperative bronchial artery CTA examination is a protective factor in preventing hemoptysis, which can intuitively and non-invasively determine the origin and number of blood supply arteries during hemoptysis. It has a high guiding value in finding non-bronchial systemic circulation blood supply arteries and aberrant bronchial arteries. Furthermore, it plays a leading role in the treatment of hemoptysis with BAE and helps reduce the risk of thromboembolism leakage and recurrent hemoptysis. Therefore, preoperative bronchial artery CTA examination can be performed when conditions permit, and this result has been recognized by many relevant physicians.[24-26] In addition, the present study results also revealed that the recurrence time of hemoptysis in patients without CTA examination before BAE was shorter than six months [4.8 (1.6) months] which may be related to vascular thrombosis and leakage. In summary, early recurrence (within six months) of hemoptysis after interventional treatment may be related to the leakage of blood vessels, while long-term recurrence is mostly related to the progression of the disease, leading to the regeneration of new blood vessels.

In addressing the recurrence of hemoptysis following interventional therapy, our approach has been to offer patients a repeat BAE. Our findings demonstrated that the recurrence rate of hemoptysis after the second BAE was an impressively low 3.63%. This clearly indicates that the effect of the second interventional therapy is significantly better than that of the first.

The implementation of repeat BAE presents a promising solution for managing recurrent hemoptysis. It not only shows remarkable effectiveness in reducing the recurrence rate but also offers enhanced therapeutic benefits for patients. This approach provides a new perspective and strategy in the field of treating hemoptysis recurrence after interventional therapy.

This study has limitations as it is a retrospective analysis from a single center with a small sample, potentially having recall bias and reducing result reliability. Future prospective multicenter randomized controlled studies are recommended for more reliable results. In conclusion, tumor-related hemoptysis, pleural thickening, and bilateral lung diseases are risk factors for hemoptysis recurrence after intervention. Preoperative CTA examination is a factor against hemoptysis recurrence. Early recurrence (within six months) may be due to vascular leakage. Long-term recurrence is mostly related to disease progression and new blood vessel regeneration.

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