

Prognosis and Predictors of Rebleeding After Bronchial Artery Embolization in Patients with Active or Inactive Pulmonary Tuberculosis

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Abstract

Introduction The aim of this study was to characterize the prognosis and identify factors that contribute to rebleeding after bronchial artery embolization (BAE) in patients with active or inactive pulmonary tuberculosis (PTB).

Methods Following a retrospective review, 190 patients had hemoptysis requiring BAE due to PTB in one hospital between 2006 and 2013.

Results The median age at the time of diagnosis of PTB was 37 years and 54 years at the time of first episode of hemoptysis. Among 47 patients (24.7 %) who experienced rebleeding after BAE during the median follow-up period of 13.9 months [interquartile range (IQR) 2.3–36.0 months], bleeding recurred in 12 patients (6.3 %) within 1 month and in 15 patients (7.9 %) after 1 year. The median non-recurrence time was 8.6 months (IQR 1.2–27.6 months). Independent predictors of rebleeding after BAE were tuberculous-destroyed lung [hazard ratio (HR) 3.0; 95 % confidence interval (CI) 1.5–6.2; $p = 0.003$], the use of anticoagulant agents and/or antiplatelet agents (HR 2.6; 95 % CI 1.1–5.8; $p = 0.022$), underlying chronic liver disease (HR 2.7; 95 % CI 1.1–6.9; $p = 0.033$), elevated pre-BAE C-reactive protein (CRP) (mg/dL) (HR 2.4; 95 % CI 1.0–5.5; $p = 0.048$), and the existence of fungal ball (HR 2.1; 95 % CI 1.0–4.3; $p = 0.050$).

Conclusions The risk of rebleeding after BAE in active or inactive PTB was high, particularly in patients with tuberculous-destroyed lung, chronic liver disease, the use of anticoagulant agents and/or antiplatelet agents, elevated pre-BAE CRP, and the existence of fungal ball.

Keywords Bronchial artery embolization · Pulmonary tuberculosis · Hemoptysis · Rebleeding

Abbreviations

PTB Pulmonary tuberculosis
BAE Bronchial artery embolization
IQR Interquartile range
HR Hazard ratio
CRP C-reactive protein

Introduction

Life-threatening or chronic recurrent hemoptysis is one of the most serious complications of pulmonary tuberculosis (PTB). PTB is the leading cause of hemoptysis in Korea, which is known to have an intermediate prevalence of tuberculosis [1]. There is a relatively high prevalence of hemoptysis even in patients with inactive PTB in Korea. PTB can cause extensive progressive destruction of one or both lungs and the development of post-tuberculosis sequelae including tuberculous-destroyed lung. Most patients with active or inactive PTB are not surgical candidates because of poor pulmonary function and other comorbid diseases. Recently, the success rate of bronchial artery embolization (BAE) has been very high due to technical advances and diversification of embolic material [2, 3].

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BAE has been used as an effective, non-surgical alternative to control massive or chronic recurrent hemoptysis.

Hemoptysis due to PTB can recur even after effective treatment including BAE because post-tuberculous sequelae can be permanent and lead to continuous inflammation. In addition, the recurrence of hemoptysis in patients with chronic PTB is more common than those in patients with bronchiectasis [4]. Previous studies have attempted to find risk factors for recurrent hemoptysis after BAE; there is evidence that recurrent hemoptysis is associated with the presence of a fungal ball [1, 5–7], incomplete embolization [8], active PTB [4], diabetes mellitus [6], and systemic-pulmonary artery shunts on angiography [6, 9–11]. It is important for clinicians to define risk factors of rebleeding after hemoptysis treatment in order to optimize management and follow-up for patients with hemoptysis in clinical practice. Several studies have focused on patients with active or inactive PTB. However, those reports are limited by several factors including small study populations and outdated data.

The aims of this study were to investigate the clinical features and outcomes of BAE with regard to the management of hemoptysis in patients with active or inactive PTB, and to identify risk factors associated with rebleeding after BAE in these patients.

Patients and Methods

We retrospectively reviewed the records of 288 patients who underwent BAE due to hemoptysis between January 2006 and June 2013 at Ewha Woman's University Medical Center in Seoul, South Korea. We reviewed patient medical records and radiologic findings to analyze causes of hemoptysis. Subjects who had pneumonia, bronchiectasis, lung cancer, and/or structural abnormalities per radiologic findings were excluded. In total, 190 patients who had active PTB or an episode of PTB with post-tuberculous sequelae were included in this study. The retrospective review of medical records and radiographic findings was approved by the Institutional Review Board of Ewha Medical Center (14-03A-01).

Following a review of the medical records, information on the activity of PTB, age at the time of BAE, age at diagnosis of active PTB, gender, comorbidities, laboratory findings, acid fast bacilli (AFB) smear and culture results, and admission to the intensive care unit at first BAE were obtained. All included patients underwent chest X-ray and chest-computed tomography (CT), and 128 patients underwent bronchoscopic evaluation at first BAE. The results of the review were confirmed by two chest radiologists and

at least two pulmonologists. All patients were classified by radiologic findings and AFB staining at the time of first BAE [12, 13]. Active PTB cases were defined as both bacteriologically confirmed cases and clinically diagnosed cases based on the WHO definitions [14]. Post-tuberculous sequelae were defined as a previous history of PTB with AFB negativity, with or without imaging suggesting inactive TB including calcified nodule, bronchiectasis, fibrosis, and fungal ball. The designation of tuberculous-destroyed lung was based on a clear history of present or past tuberculosis, coupled with radiologic findings of destroyed lung parenchyma, lung volume loss, and/or secondary bronchiectatic changes, all of which were verified by chest radiology via chest X-ray and CT [15, 16].

Between January 2006 and June 2013, 190 consecutive patients underwent BAE, performed by two interventional radiologists, due to active or inactive PTB. A catheter was introduced into the right femoral artery mainly using a 5-French guiding catheters. The choice of embolization method and material was made by each individual interventional radiologist. We classified vessel hypertrophy, systemic-pulmonary shunting, and neo-vascularization based on angiogram findings and reviewed the number of embolized arteries and arterial distribution. Agents used for embolization included coils, gelfoam, polyvinyl alcohol (PVA), or a combination of the above materials. The success of BAE was defined as confirmation of significantly reduced blood flow on angiography and of no recurrence of hemoptysis (not including blood-tinged sputum) within 24 h after first BAE [17]. Rebleeding was defined as the need for a second BAE as deemed by the clinician 24 h after the first procedure. Survival and recurrent hemoptysis were identified from the medical record, by interviews with patient families or doctors or by accessing national death registry data. Time zero was set as the date of first BAE. The recurrence-free time was calculated from the first BAE to the second BAE and to the patient's death or last follow-up in this hospital. The median follow-up period was 13.9 months [interquartile range (IQR) 2.3–36.0 months].

For statistical analysis, SPSS 21.0 software (SPSS Inc., Chicago, IL) was used throughout the study. $p < 0.05$ was taken to indicate statistical significance. Continuous variables were analyzed by calculating the mean, standard deviation, median, and IQR. Recurrence-free probabilities were estimated using the Kaplan–Meier method, and the log-rank test was applied to compare the time to recurrence curves according to patient characteristics. Cox proportional hazard multivariate analysis was performed to identify independent factors associated with the recurrence of hemoptysis. Hazard ratios (HR) with 95 % confidence intervals (CI) were used to report the results.

Results

The characteristics of the 190 patients are summarized in Table 1. The median age at the time of first BAE was 54 years (IQR 45–66 years), and 136 patients (72 %) were male. The most frequently comorbid condition was hypertension ($n = 47$; 25 %), followed by diabetes mellitus ($n = 31$; 16 %) and chronic liver disease ($n = 20$; 11 %). Twenty-eight (15 %) patients required long-term maintenance therapy with anticoagulant agents and/or antiplatelet agents because of ischemic heart disease and/or cerebral vascular disease. The median age at the time of first diagnosis with active PTB was 37 years; 40 (21 %) patients were diagnosed with active PTB at the first visit to our institution due to hemoptysis. Life-threatening hemoptysis requiring admission to the intensive care unit occurred in 46 patients (24 %), with 22 patients necessitating mechanical ventilation. Patients were categorized by whether or not recurrent hemoptysis developed after BAE.

Recurrent hemoptysis occurred in 47 of 190 patients (25 %). The overall clinical outcomes in patients with rebleeding after BAE are summarized in Table 2. All 47 patients who had recurrent hemoptysis were preferentially managed with repeated BAE with a median number of BAE of 2 (range 2–7 times). The median time interval between the first and second BAE was 7.0 months (range 0.7–81.6 months). Among 47 patients in the rebleeding

Table 2 Recurrent hemoptysis after bronchial artery embolization

	$n = 190$
Recurrent hemoptysis after BAE	47 (25)
Overall counts of BAE	2 (range 2–7)
Interval between 1st BAE and rebleeding	8.7 months (1.2–27.6)
Time interval to recurrence of hemoptysis after 1st BAE ^a	($n = 47$)
<1 month (early onset)	12 (26)
>1 year	15 (32)
Operation	9 (5 %) ^b
Total mortality	15 (8 %)
Death due to hemoptysis	5 (3 %)

Data are medians (interquartile range), or frequency (%)

BAE bronchial artery embolization

^a No recurrence until October 31, 2013

^b Three patients underwent surgery after 1st BAE

group, 12 patients (26 %) underwent repeated BAE within one month and 15 patients (32 %) after one year from the first procedure. Surgical resection was performed in nine of 47 patients (19 %) for control of recurrent massive hemoptysis; among them, three patients underwent surgery for a second episode of hemoptysis after immediate control of the second BAE.

During the follow-up period, the group who experienced rebleeding tended to be of younger age at the time of the

Table 1 Clinical characteristics of patients with active pulmonary tuberculosis or post-tuberculosis sequelae

Variable	Total ($n = 190$)	Non-recurrence ($n = 143$)	Recurrence ($n = 47$)
Age at admission (years)	54 (45–66)	64 (45–74)	55 (38–71)
Male:Female	136 (72):54	98:45	38:9
Comorbidity			
Hypertension	47 (25)	36	11
Diabetes mellitus	31 (16)	23	8
Chronic liver disease	20 (11)	13	7
End-stage renal disease	2 (1)	1	1
Use of anticoagulant and/or antiplatelet agents	28 (15)	19	9
Age at first diagnosis of active pulmonary tuberculosis	37 (28–50)	47 (28–50)	27 (25–44)
Active pulmonary tuberculosis	40 (21)	35	5
Reactivated status of tuberculosis	23 (12)	17	6
Initial ICU admission	46 (24)	32	14
Mechanical ventilator applied	22 (12)	14	8
Laboratory finding			
Hemoglobin (g/dL)	12.7 (11.2–14.0)	12.7 (11.6–14.3)	12.9 (11.1–15.3)
White blood cell ($10^3/\mu\text{L}$)	8100 (6100–10,300)	10,500 (6365–13,500)	7880 (7480–11,700)
Platelet ($10^3/\mu\text{L}$)	229 (192–274)	195 (147–217)	213 (209–281)
C-reactive protein (mg/L) ($n = 171$)	0.70 (0.23–3.64)	0.75 (0.24–3.07)	4.12 (1.96–6.60)

Data are medians (interquartile range), or frequency (%)

ICU intensive care unit

first episode of hemoptysis and at first diagnosis of active PTB compared with those in the non-recurrence group, but there was no significant difference ($p = 0.235$). No significant difference was found with respect to gender ratio, coexisting medical problems, activity of PTB, or the need for ICU admission with/without mechanical ventilation during the first episode of hemoptysis between patients in the non-recurrence group and those in the rebleeding group. Although the level of C-reactive protein (CRP) (mg/dl) at the first episode of hemoptysis before first BAE was elevated in the group with recurrent hemoptysis in comparison with the non-recurrence group, this difference was not significant (4.12 vs. 0.75 mg/L, $p = 0.070$) (Table 1).

Subjective symptomatic improvement was achieved in all patients immediately after the first BAE procedure. There were no procedure-related spinal complications or mortalities. Overall mortality was 8 % (15/190), and hemoptysis-related mortality was 3 % (5/190). Ten patients died of other causes such as septic shock ($n = 3$), ischemic heart disease ($n = 3$), aspiration pneumonia ($n = 2$), liver failure due to hepatocellular carcinoma ($n = 1$), and sudden arrest with unknown cause ($n = 1$) (Table 2).

Chest CT scans were performed prior to the procedure, and bronchial angiography was performed during BAE in all patients (Table 3). On retrospective analysis of chest CT findings, the right lung field was found to be the most common combined site, and the most common findings were hypertrophied vessels and parenchymal consolidation. PTB complications such as a fungal ball and tuberculous-destroyed lung were more frequently observed in patients in the rebleeding group. Similarly, hypertrophied vessels and lung parenchymal consolidation were also more common in the recurrence group. The most common angiographic findings were hypertrophied vessels and neovascularization. The number of embolized arteries was classified into one vessel alone and more than two vessels; there was no significant difference between the two groups. The distribution of embolized arteries was predominantly in the right lung. Most patients received PVA as an embolic agent during BAE (97 %). There was no significant difference in the type of embolic agent used between the two groups.

Suspected factors were evaluated with regard to their influence on recurrence-free time after BAE using Kaplan–Meier survival curves and then were compared using log-rank tests. Three factors were associated with recurrence-free time after BAE based on Kaplan–Meier survival curves and log-rank tests ($p < 0.05$): tuberculous-destroyed lung ($p < 0.001$), the existence of fungal ball on chest CT ($p = 0.002$), and elevated pre-BAE CRP (mg/dl) above the normal range ($p = 0.020$) (Fig. 1). After adjusting for age, gender, presence of underlying comorbidities, activity status of PTB, need for ICU admission, angiography

findings, and the number of embolized arteries, these three factors were introduced into a Cox regression hazard model using a backward-selection method, which revealed that tuberculous-destroyed lung (HR 3.0; 95 % confidence interval (CI) 1.5–6.2; $p = 0.003$), underlying chronic liver disease (HR 2.7; 95 % CI 1.1–6.9; $p = 0.033$), the use of anticoagulant agents and/or antiplatelet agents (HR 2.6; 95 % CI 1.1–5.8; $p = 0.022$), and elevated CRP above the normal range pre-BAE (HR 2.4; 95 % CI 1.0–5.5; $p = 0.048$) were independent pre-dictive factors for rebleeding after BAE. And the existence of a fungal ball (HR 2.1; 95 % CI 1.0–4.3; $p = 0.050$) was a predictor for rebleeding after BAE with marginal significance (Table 4).

Discussion

This study showed that several factors were associated with recurrent hemoptysis in patients with active or inactive PTB who underwent initial BAE including the existence of fungal ball, tuberculous-destroyed lung, and other previously known risk factors. Moreover, clinical factors such as inflammation suggested by elevated CRP level prior to first BAE, use of anticoagulation agents, and the presence of underlying chronic liver disease (median platelet count, 218,000/mm³; international normalized ratio (INR), 1.06) were found to significantly affect rebleeding after BAE due to PTB. BAE is considered an initial treatment for control of hemoptysis in TB patients with an immediate success rate of about 90 % [2]. Previous studies have reported approximately 10–33 % recurrence in hemoptysis patients [2], with studies performed in Korea among PTB patients reporting rates of 30.6 % [1] and 40.3 % [6]. Although our study included only PTB patients, the frequency of rebleeding was 25 %, which is lower than that reported in previous studies. The frequency may be reduced due to differences in the research period and technical developments such as advancements in embolic materials [10, 18]. Most patients with active PTB associated with hemoptysis are favorable candidates for treatment [7]. Lee et al. [4] reported that active PTB status was associated with recurrence after BAE. However, Shin et al. [1] reported that recurrent hemoptysis was more frequent in reactive PTB patients, and Hwang et al. [6] showed that PTB activity was not associated with rebleeding after BAE. In this study, TB activity was not associated with recurrent hemoptysis after BAE. This discrepancy may be related to differences in TB prevalence geographically, differences in the start time of the study, and differences in the composition of the study population. Therefore, further large-scale studies are warranted.

Similar to previous studies, our study showed that recurrent hemoptysis after BAE was associated with chest

Table 3 Summary of CT findings and embolization of vessels

	Total (n = 190)	Non- recurrence (n = 143)	Recurrence (n = 47)
Chest CT finding			
Extent			
Focal area of involvement	59	50	9
Right lung involvement	89	71	18
Left lung involvement	50	34	16
Bilateral lung involvement	51	38	13
Fungal ball	25 (13)	12	13*
Active tuberculosis	63 (33)	52	11
Tuberculous-destroyed lung	64 (34)	36	28*
Hypertrophied vessel	149 (78)	107	42*
Consolidation	146 (77)	103	43*
Finding of angiogram			
Broncho-pulmonary artery shunt	35 (18)	27	8
Vessel hypertrophied	187 (94)	133	45
Neo-vascularization	133 (70)	101	32
Number of embolized arteries			
1 vessel	98 (52)	74	24
≥2 vessels	92 (54)	69	24
Distribution of abnormal arteries			
Bronchial artery	178 (94)	133	45
Right:left:both	94:41:43	69:31:33	25:10:10
Non-bronchial artery	54 (27)	41	13
Right:left:both	39:7:6	32:5:3	7:2:3
Embolic agents			
PVA agent	185 (97)	140	45

Data are frequency (%)

PVA polyvinyl alcohol

* $p < 0.05$

CT findings of TB-destroyed lung [15] or a fungal ball [1, 5–7] as complications of PTB. The presence of a fungal ball is associated with a higher incidence of rebleeding and mortality because extensive parasite circulation from different sources is likely to be associated with vasculitis in cases of thick vascular cavity wall, making complete devascularization difficult [1, 10]. In addition, tuberculous-destroyed lung [15, 16] is a poor prognostic factor of massive hemoptysis that is associated with increased mortality. Goh et al. [10] and Mossi et al. [9] suggested that a mycetoma, non-bronchial blood supply, and systemic-pulmonary artery shunt are related to rebleeding. In Korea, Lee et al. [4] reported that chronic PTB patients with non-bronchial arteries more frequently experienced recurrent hemoptysis. However, this has not been confirmed by other studies. The frequency of non-bronchial systemic

circulation is known to be approximately 10–30 % [8, 11]. In our study, the frequency was 27 % and was not significantly associated with recurrence. When a systemic-pulmonary artery shunt is found on angiogram, rebleeding has been more frequently reported in previous studies conducted in Korea [6] and Japan [11], but there was no relationship detected in this study.

Since previous studies primarily focused on combined status or the radiologic perspective, there are few known clinical risk factors for recurrent hemoptysis in PTB patients. Hwang et al. [6] reported that diabetes mellitus (DM) was significantly associated with recurrence after BAE, and DM was found to be a poor prognostic factor in PTB patients in another study [19]. In our study, 16 % patients had DM, which was not a comorbidity significantly associated with recurrence after BAE. However, patients taking anti-coagulant agents [20], or antiplatelet agents [21], which have the known side effect of increased bleeding risk, showed unfavorable results with rebleeding after initial BAE. In this study, 12 patients were taking anticoagulant agents, and 17 were taking the antiplatelet agents. Only one patient was taking combination therapy for management of atrial fibrillation and cerebral vascular accident. Although we analyzed each agent of anticoagulant agents and antiplatelet agents, we did not identify a trend toward increasing rebleeding risk for any individual agent. Likewise, patients with chronic liver disease which is known to cause coagulation abnormalities, were also shown to have a higher incidence of rebleeding [22]. However, these may not necessarily be poor prognostic factors, because of the limited number of patients with the described medical conditions.

Among the laboratory parameters investigated, an elevated CRP level above the normal range prior to initial BAE, signifying active inflammation, was confirmed as a significant risk factor for recurrent hemoptysis. There have been few reports on the laboratory findings associated with hemoptysis. CRP is an indicator of acute inflammation and is a well-known risk factor associated with cardiovascular disease [23], colon cancer [25], and inflammatory bowel disease [25]. Clinically, CRP is an index us to determine the severity of inflammation such that a higher CRP level indicates more severe inflammation [26]. Therefore, patients with lung inflammation combined with hemoptysis are at increased risk for rebleeding after initial BAE and so will need treatment not only for bleeding control during BAE but also appropriate medical treatment and follow-up. However, we did not assess CRP level on follow-up after treatment, which limits our interpretation of its significance as a risk factor. Still, in addition to serving as an acute inflammatory marker, CRP may also be a chronic inflammatory marker because post-tuberculous sequelae are permanent and can cause continuous pulmonary inflammation.

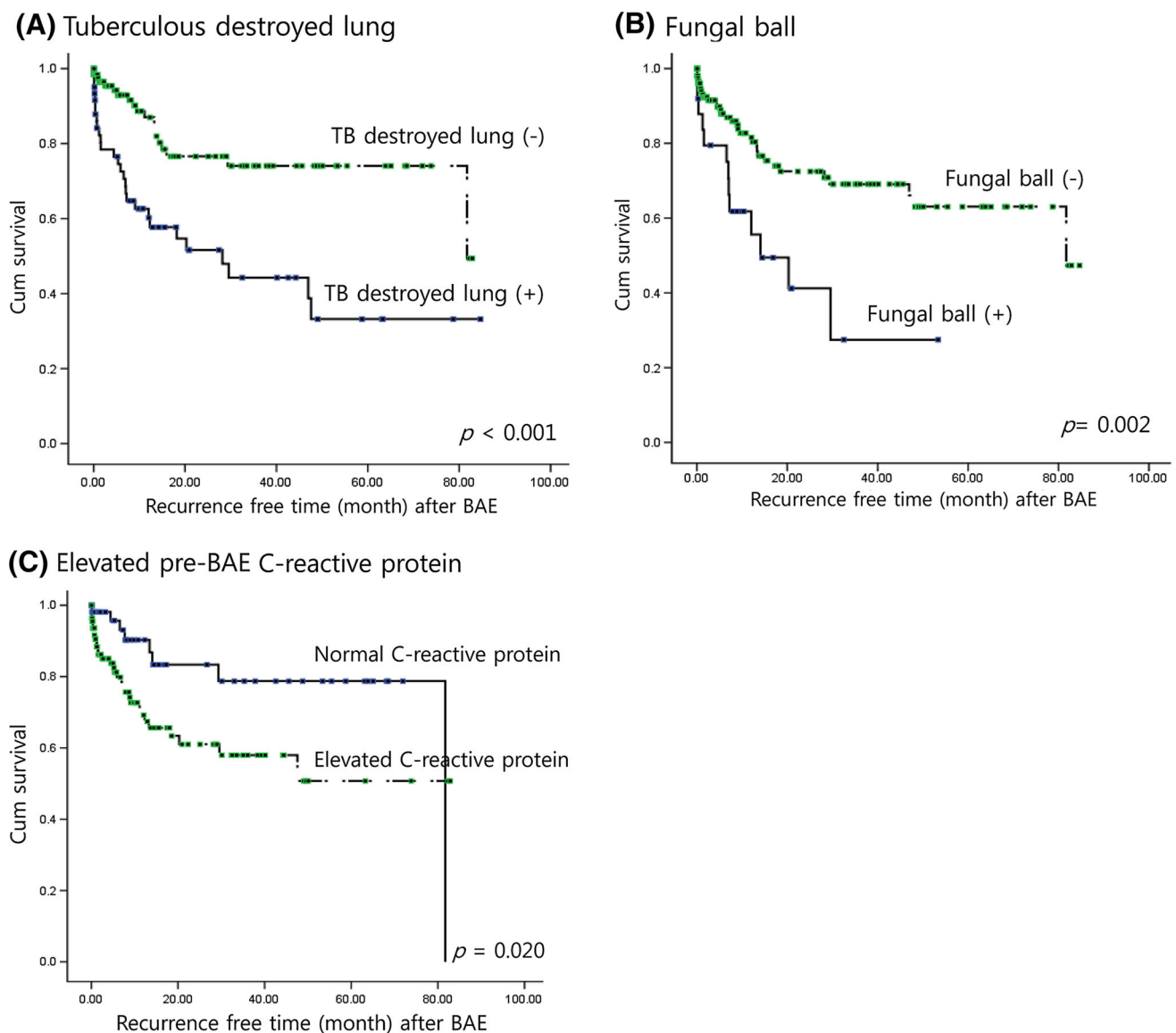


Fig. 1 Time to recurrence curves as depicted by the Kaplan–Meier method

Table 4 Analysis of risk factors associated with recurrent hemoptysis after bronchial artery embolization

	Hazard ratio (95 %) with CI	<i>p</i> value
Tuberculous destroyed lung	3.027 (1.476–6.208)	0.003
Use of anticoagulation agents and/or antiplatelet agents	2.567 (1.143–5.767)	0.022
Chronic liver disease	2.725 (1.084–6.854)	0.033
Elevated pre-BAE C-reactive protein	2.363 (1.007–5.544)	0.048
Fungal ball	2.069 (1.000–4.282)	0.050

Cox proportional hazards model was used with the backward-elimination method with forced inclusion of variables significant in clinically associated factors

BAE bronchial artery embolization, CI confidence interval

The technique of BAE has been improved in recent years by the use of super-selective micro-catheters, more thorough angiographic search methods and more effective

embolic materials [2]. Among all patients, 96 % of patients underwent BAE using a micro-catheter and PVA as embolic agents. Although an incomplete study of BAE is a

well-known risk for rebleeding [8], there were no incomplete procedures in this study and we confirmed the success of the first BAE by ensuring blood flow was decreased on angiogram immediately after BAE. BAE was a safe and effective treatment for hemoptysis, even considering the risk of rebleeding. Through the recent development of advanced chest CT and interventional skills, interventional radiologists can assess non-pulmonary artery distribution or abnormal vascular anatomy. These advancements are expected to further reduce rates of BAE failure or incomplete studies.

Our study has several limitations related to its retrospective nature and inclusion of cases from only one tertiary hospital. However, our study included relatively recent cases of BAE and was designed to reduce technical bias, since the use of PVA and confirmation of angiography after BAE are close to the standard method of BAE. In conclusion, BAE is an effective and safe intervention in cases of hemoptysis due to PTB in Korea, which is known to have an intermediate prevalence of TB. Importantly, this study suggested that when BAE is performed, it should be followed by risk assessment for rebleeding. The risk of rebleeding after BAE in active or inactive PTB was higher in patients with tuberculous-destroyed lung, chronic liver disease, the use of an anticoagulant and/or an antiplatelet agent, elevated pre-BAE CRP as an inflammatory marker, or the presence of fungal ball. It is essential to provide close follow-up in such patients after initial BAE and to ensure appropriate medical management.

Conflict of interest The authors have no financial or non-financial conflict of interest with regard to any company referred to in this article.

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