ROLE OF COMORBID RISK FACTORS OF TUBERCULOSIS IN BRONCHIAL ARTERY EMBOLISATION FOR MANAGING MASSIVE HAEMOPTYSIS

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ABSTRACT

BACKGROUND

Among the multiple causes of haemoptysis, active tuberculosis (TB), chronic inflammatory lung diseases due to bronchiectasis, aspergilloma within a chronic sarcoid or tuberculous cavity are the most common cause of haemoptysis in developing countries. Several diseases increase the risk of tuberculosis causing increased morbidity and mortality among these patients.

The following study was intended to evaluate the role of comorbid risk factors in bronchial artery embolisation (BAE) for managing haemoptysis.

MATERIALS AND METHODS

282 patients who presented with massive haemoptysis were included in the study, 141 over a period of 2 years from April 2012 to April 2014. Further followup of all the patients for 2 years from April 2014 to April 2016 by dividing the patients based on tuberculosis and comorbid risk factors. Recurrent bleeding and mortality were evaluated among the patients.

RESULTS

55 patients (40%) with tuberculosis, 28.3% of patients with bronchiectasis and fibrocavitary lesion of lung, 7.8% of patients with aspergilloma underwent BAE. Comorbid risk factors mainly were DM in 15.6% and HIV in 9.9% of patients. Haemoptysis free survival rate in TB patients along with comorbid risk factors were 64.4%, 55.2% and 41.2% in 6, 12 and 24 months respectively. Whereas in non-tuberculous conditions it was 81.3%, 77.1% and 68.1% in 6, 12 and 24 months respectively and in tuberculosis alone without any risk factors it was 98.1%, 91.2% and 88.1% in 6, 12 and 24 months respectively which showed a statistical significance ($p = 0.05$). Mortality rate was significantly high in TB along with comorbid risk conditions group when compared to the rest of the groups ($p = 0.05$).

CONCLUSION

Prognosis of the TB patients without comorbid risk factors were good when compared to TB along with risk factors for BAE for massive haemoptysis. The risk factors namely diabetes mellitus (DM), human immunodeficiency virus (HIV), chronic liver diseases, chronic renal diseases and coronary artery diseases not only play an important in the activation of latent infection, but also causes increased mortality in these patients. So these risk factors can also be considered as comorbidities in these patients increasing the risk of recurrent haemoptysis and mortality of patients undergoing BAE for massive haemoptysis.

KEYWORDS

Bronchial artery embolisation (BAE), massive haemoptysis, pulmonary tuberculosis (TB), diabetes mellitus (DM), human immunodeficiency virus (HIV).

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BACKGROUND

Definition of Haemoptysis

Haemoptysis or the expectoration of blood from the lower respiratory tract^{1,2} can range from blood-streaking of sputum to the presence of gross blood in the absence of any accompanying sputum.

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The definition of massive haemoptysis varies widely in the literature from 200 mL to 1000 mL/24 hrs,^{3,4} but the expectoration of ≥ 600 mL in 24 hrs. is what most authors use in clinical reports to define massive haemoptysis.⁵

It is estimated that 400 mL of blood in the alveolar space is sufficient to cause significant hindrance to the oxygen transfer,⁶ although only minor changes in the vital signs will be noted for the same amount of blood loss.⁷

Massive haemoptysis is usually a sign of an underlying chronic disease.⁸

Active tuberculosis (TB) continues to be the leading cause of haemoptysis worldwide.⁹ In some cases, 'a cause' cannot be found and is termed idiopathic or cryptogenic haemoptysis. It is a diagnosis of exclusion and is reported to be responsible for 3% - 42% of haemoptysis episodes, particularly in smokers.¹⁰

Documented mortality rates following surgical intervention vary between 7.1% and 18.2%, but increase to 40% in certain emergency conditions.¹¹ Larger number of patients with haemoptysis are not suitable candidates for surgery due to pre-existing comorbidities and poor respiratory reserve. However, surgery remains the treatment of choice for the treatment of massive haemoptysis caused by iatrogenic pulmonary artery rupture, trauma to chest and aspergilloma resistant to other treatment options.¹² BAE has become a well-established interventional vascular technique for the management of massive and recurrent haemoptysis.^{13,14} The survey by the American College of Chest Physicians showed that a higher proportion of chest physicians favoured interventional radiology over either conservative or surgical management.¹⁵

BAE of bronchial and non-bronchial systemic arteries is now a well-known procedure for the control of massive and recurrent haemoptysis. Immediate control of haemoptysis is achieved in 73% - 99% of treated patients. However, recurrent haemoptysis is common, occurring in 10% - 55%.^{14,15,16}

Even though BAE in TB patients has been studied previously,^{17,18} these studies have limited number of patients with tuberculosis as the aetiological factor for massive haemoptysis and the results have not been sufficient to address the role of BAE in pulmonary tuberculosis patients having comorbid risk factors. Our study was intended to evaluate recurrence of haemoptysis and mortality of the patients undergoing BAE.

The burden of tuberculosis and cardiovascular disease (CVD) are rapidly increasing in low- and middle-income countries like India.¹⁹ Many public health programs are challenged with the overlapping tuberculosis and CVD epidemics.²⁰ Recent epidemiologic work has shown that the risk of cardiovascular diseases among the persons who develop tuberculosis is higher than in persons without a history of tuberculosis, even several years after recovery from tuberculosis.²¹

Aims and Objectives

The present study was intended to evaluate the role of various co-morbid risk factors in bronchial artery embolisation (BAE) for managing haemoptysis.

MATERIALS AND METHODS

It is a retrospective study intended to evaluate the role of comorbid risk factors in bronchial artery embolisation (BAE) for managing haemoptysis among the three cohorts namely-

- 1) Patients suffering from tuberculosis alone without any comorbid risk factors (TB group).
- 2) Patients having comorbid risk factors along with tuberculosis (TB + comorbid).
- 3) Patients having non-tuberculosis pulmonary disease (Non-TB).

Study Design

The following study is a retrospective observational and analytical cohort study for two years among the patients admitted for massive haemoptysis undergoing bronchial artery embolisation.

Study Group

Out of the 282 patients who presented with massive haemoptysis, 141 patients were included in the study after

fulfilling the inclusion criteria from April 2012 to April 2014. Followup of patients for two years from April 2014 to April 2016 were done after undergoing bronchial artery embolisation.

The analytical component of the study aims to determine if tuberculosis infection adversely affected the outcome of the procedure.

Inclusion Criteria

- 1) Patients from whom biological specimen was positive by smear microscopy, culture or WHO-approved rapid diagnostic test (such as Xpert MTB/RIF) for the diagnosis of pulmonary tuberculosis.
- 2) Patients in whom the first and second attempts of bronchial artery embolisation were done.
- 3) Patients in whom surgical intervention is not possible for the following disease conditions like lung abscess, bronchiectasis, bronchogenic carcinoma, cystic fibrosis or pneumonia.

Exclusion Criteria

- 1) Third or subsequent bronchial artery embolisation attempted for the same patient.
- 2) Multidrug resistant tuberculosis and extensive drug tuberculosis patients (MDRTB/ XDR-TB).
- 3) Patient less than 14 years old.

Statistical Analysis

Data analysis was done by SPSS 24.0 (SPSS, IBM, USA) were used for statistical analysis. Chi-square test was used for categorical data for comparing control of bleeding (yes) and no control of bleeding (no) among the three treatment arms.

Cumulative recurrent haemoptysis free rate and cumulative survival rate were evaluated individually using a Kaplan-Meier survival analysis. Log-rank test was performed to determine the significance between the three groups. Univariate and multivariate analysis was performed to determine risk factors of recurrent haemoptysis and mortality.

Cox proportional hazard model was used to estimate hazard ratio (HR) for recurrent haemoptysis and mortality between two groups. Multiple variables were calculated in the form of mean value $\pm$ standard deviation. P value less than 0.05 was measured to be statistically significant among the groups.

RESULTS

Of the 282 patients who presented with massive haemoptysis, 141 patients underwent bronchial artery embolisation (BAE). Majority of the patients (79) (Table 0.5) were male (56.2%). The basic demographic properties of the included patients were shown in Table A.

The age of the patients included in our study were between 15 - 70 years with an average of mean age of 46.01 years. The majority of the members were between 50 - 59 years of age and minority of the patients were between 14 - 19 years. Most of the patients (71.1%) have BMI < 18.5 kg/m² (Table 0.5 and 1) when compared to patients (28.9%) having BMI > 18.5 kg/m². Among the pulmonary tuberculosis cohort, 3 (2.1%) patients were sputum positive, 2 (1.4%) patients were culture positive and 2 (1.4%) patients were diagnosed based on nucleic acid amplification tests like Xpert MTB (TB NAAT) (Table 1). Diagnoses of 2 (1.4%) patients were done

based on the radiological findings. Total number of patients suffering with tuberculosis without any comorbid risk factors were 9 (6.3%); 46 (32.6%) patients were having comorbid risk factors along with tuberculosis. Among the comorbid risk factors, diabetes mellitus was associated with 22 (15.6%) patients followed by HIV in 14 (9.9%) patients. Majority of the patients (55:40%) in study were suffering from tuberculosis (TB + TB comorb).

Rest of the 86 (60%) patients were suffering from other non-tuberculous lung diseases, namely fibrocavitary lung disorders and bronchiectasis in 40 (28.3%), aspergilloma in 11 (7.8%) patients, lung cancer in 9 (6.3%) and pneumonia in 12 (8.5%) patients (Table 1).

Variables	PTB alone	PTB + Comorbid	Non-Tuberculosis	P value
Gender				
Male	05 (3.5%)	25 (17.1%)	49 (34.7%)	P >0.05
Female	04 (2.8%)	21 (14.8%)	37 (26.2%)	
Age (Mean)	43	45	50	P >0.05
Body mass index (m)				
>18.5	03 (2.1%)	25 (17.7%)	13 (9.2%)	P<0.05
<18.5	06 (4.2%)	21 (14.8%)	73 (51.7%)	
Smokers				
Non-smokers/ ex-smokers	23 (16.3%) 21 (14.8%)	25 (17.7%) 24 (17.0%)	33 (23.4%) 14 (9.0%)	P<0.05

Table 0.5. Demographic Characteristics of the Patients

Demographics		Total Cases
Age (Years)		Mean Age 46.01
Gender	Male: Female	79 (56.2%) 62 (43.8%)
Body mass index (BMI)	>18.5: <18.5	41 (28.9%) 100 (71.1%)
Smoking history	Smoker/ Ex-smoker Never smoked	81 (57.9%) 60 (42.1%)
Pulmonary Tuberculosis (n= 9)	Sputum positive Culture positive TB NAAT positive	3 (2.1%) 2 (1.4%) 2 (1.4%)
Tuberculosis + Comorbid conditions (n= 46)	TB + Immuno.S TB+DM TB+HIV TB+LIVER.D TB+CVD TB+CKD	2 (1.4%) 22 (15.6%) 14 (9.9%) 2 (1.4%) 2 (1.4%) 3 (2.1%)
Non-TB (n= 86)	Fibrocavitary/ Bronchiectasis Aspergilloma Lung abscess Lung cancer Pneumonia Others	40 (28.3%) 11 (7.8%) 06 (4.2%) 09 (6.3%) 12 (8.5%) 08 (5.6%)

Table 1. Demographics of all the Patients included in the Study

CVD: Cardiovascular disease, CKD: Chronic kidney disease, NAAT: Nucleic acid amplification test like Xpert MTB.

The events that occurred after the procedure were divided in the following way In Less than two weeks (Figure 1)

In our series, recurrent haemoptysis occurred within 2 weeks in 14 (9.9%) of 141 patients after undergoing BAE; 11 (7.8%) patients from the TB + Comorbid group and 3 (2.1%) patients from Non-TB group (Fig. 1). Among the 11 patients 5 (3.5%) patients were diagnosed with TB along with DM, 2 (1.4%) were HIV seropositive and 2 (1.4%) patients had cardiovascular diseases (CVD) and 2 patients were on dialysis for chronic kidney disease (CKD).

In non-TB group 2 (1.4%) had bronchiectasis, 1 (0.7%) patient had bronchogenic carcinoma who died before 2nd re-embolisation due to excessive blood loss.

Bleeding resolved spontaneously with conservative management before 2nd re-embolisation in 1 patient belonging to TB + comorbid group (Fig. 1).

8 patients out of 11 in TB + comorbid group underwent second BAE.

2 out of 3 in non-TB patients underwent successful second BAE; 2 patients having tuberculosis and uncontrolled diabetes died within 4 days after undergoing 2nd bronchial artery embolisation.

```
graph TD
    A[1st BAE] --> B[141]
    B --> C[98 pts Success]
    B --> D[14 pts Failed]
    D --> E[11 TB + Comorb Group]
    D --> F[3 Non-TB Group]
    E --> G[1 pt TB + Comorb Group]
    F --> H[2 Non-TB Group]
    G --> I[8 pts TB + Comorb Group]
    H --> J[1 pt Non-TB Group]
    I --> K[2 pts TB + Comorb Group]
    J --> L[2 pts TB Group]
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The flowchart illustrates the study design, starting with 1st BAE (1st Bronchoalveolar Examination) leading to 141 patients. These patients are divided into two groups: 98 pts Success and 14 pts Failed. The 14 pts Failed group is further divided into 11 TB + Comorb Group and 3 Non-TB Group. The 11 TB + Comorb Group is further divided into 1 pt TB + Comorb Group and 8 pts TB + Comorb Group. The 8 pts TB + Comorb Group is further divided into 2 pts TB + Comorb Group and 2 pts TB Group. The 3 Non-TB Group is further divided into 2 Non-TB Group and 1 pt Non-TB Group.

Within 2 Weeks to 1 Month (Figure 2)

Two patients were referred for surgery. Remaining 4 (3.5%) patients from TB + Comorbid group (Fig. 2) underwent second BAE; one patient (HIV + TB) died after second BAE.

7 (4.9%) patients had recurrent haemoptysis between 1st - 3rd month of embolisation; 1 out of 7 patients was from TB group, 4 from TB + Comorbid group and 2 from non-TB group. Haemoptysis in 1 patient (TB group) resolved spontaneously and in 1 patient (non-TB group) resolved with successful antibiotic treatment.

```

graph TD
    A[1st BAE] --> B[141]
    B --> C[98 pts Success]
    A --> D[Rebleeding 2 Wks - 1 Month]
    D --> E[Rebleeding]
    E --> F[2nd BAE]
    F --> G[Deaths]
    G --> H[Surgery]
    B --> I[9 Patients]
    I --> J[1 pt TB 7 pts TB + Com]
    J --> K[1 TB + 4 pts TB + Com]
    K --> L[1 + 1 pts TB + Com]
    L --> M[2 pts TB + Com]
    B --> N[1 pt Non-TB Group]
    B --> O[1 pt Non-TB Group]
  
```

The flowchart illustrates the study design and patient outcomes. It starts with the 1st BAE, leading to 141 patients. From these 141 patients, 98 pts were successful, while 9 patients required further treatment. The 9 patients were divided into two groups: 1 pt TB and 7 pts TB + Com. The 7 pts TB + Com group was further divided into 1 TB and 4 pts TB + Com. The 1 TB group was further divided into 1 + 1 pts TB + Com. The 1 + 1 pts TB + Com group was further divided into 2 pts TB + Com. The 1 pt Non-TB Group was also included in the study.

```

graph TD
    A[1st BAE] --> B[141]
    B --> C[98 pts Success]
    A --> D[Rebleeding 1 mnth - 3 mnths]
    B --> E[7 pts Rebleeding]
    D --> F[Resolved Spontaneously]
    E --> G[1 TB + 4 TB + Com Group]
    G --> H[4 pts TB + Com Group]
    G --> I[1 pt TB Group]
    I --> J[1 pt TB + Com Group]
    G --> K[2 pts Non-TB Group]
    K --> L[1 pt Non-TB Group]
    K --> M[1 pt Non-TB Group]
    K --> N[1 pt Non-TB Group]
  
```

The flowchart illustrates the study design, starting with 1st BAE (1st Bleeding After Exposure) leading to 141 patients. From 141 patients, 98 patients were successful. The 141 patients were divided into two groups: Rebleeding 1 month - 3 months (7 patients) and Resolved Spontaneously (14 patients). The 7 patients who rebled were further divided into 1 TB + 4 TB + Com Group (4 patients) and 1 pt TB Group (1 patient). The 14 patients who resolved spontaneously were divided into 4 pts TB + Com Group (4 patients) and 1 pt TB + Com Group (1 patient). The 4 pts TB + Com Group was further divided into 2 pts Non-TB Group (2 patients) and 1 pt Non-TB Group (1 patient). The 1 pt TB + Com Group was further divided into 1 pt Non-TB Group (1 patient).

3 Months - 6 Months

6 Months - 12 Months

1 Year - 2 Years

Patient with cirrhosis of liver died before 2nd BAE; 1 patient having tuberculosis and HIV co-infection underwent surgical treatment. Remaining 5 patients underwent re-embolisation successfully.

Group		< 2 wks	2 wks - 1 mn	1 - 3 mn	3 - 6 mn	6 - 1 yr	1 - 2 yr	P value
Rebleeding	Total	14	9	7	3	3	7	
	TB Alone		1	1			1	
	TB + Comorbid	11	7	4	2	2	5	P<0.05
	Non-TB	03	1	2	1	1	1	
Resolved	TB Alone			1				
	TB + C:NTB	01		1				
Death before 2 nd BAE	TB Alone							
	TB + Comorbid	01	1				1	P<0.05
	Non-TB							
2 nd BAE	Total	10	6	5	2	2	5	
	TB Alone		1				1	
	TB + Comorbid	8	4	4	1	1	3	P<0.05
	Non-TB pts.	2	1	1	1	1	1	
Total Deaths	Total	3	2	2		1	1	
	TB Alone							
	TB + Comorbid	2	2	1		01	1	P<0.05
	Non-TB	1		1				
Surgery	All Groups	2	2		1		1	

Table 2. Events that occurred Post BAE Procedure

DISCUSSION

Haemoptysis was immediately stopped or markedly reduced in 98 patients (69.5%) after first bronchial artery embolisation; 30 (21.2%) patients subsequently underwent second bronchial artery embolisation. The overall success of bronchial artery embolisation in our study was 85.1%.

Treatment Arm	Control of Haemoptysis	No Control	Total Rows	P value
PTB	06	03	09	
TB + Comorb	15	31	46	<0.05
Non-TB	77	09	86	
Total Columns	98 (69.5%)	43 (30.4%)	141	

Table 3. Control of Haemoptysis among the Three Groups of People

The chi-square statistic is 45.856. The p-value is < 0.00001. The result is significant at p < .05.

Among the 141 patients, 43 (29.5%) experienced recurrence of bleeding during the follow-up period. Table 3 summarises the statistical results of the three groups. Among 141 patients final disease activity was classified as active TB in 9 (6.3%), TB along with comorbid conditions in 46 (32.6%) and non-tuberculosis aetiology in 86 (60.1%).

Control of bleeding is more common in non-TB and PTB patients when compared to the pulmonary tuberculosis along with co-morbid risk factors. These co-morbid risk factors are the main reason for recurrence of haemoptysis after BAE.

In most of the studies, success of BAE ranges from 73 - 99%.^{14,15} In our study, the success of BAE was 69.5% after 1st BAE; 85.1% success after 2 BAE. This is the first study to detect the role of co-morbid risk factors on BAE.

Primary Outcome: Cumulative Recurrent Bleeding Free Rate

Using Kaplan-Meier survival analysis, the bleeding free survival rates were calculated and shown in the following Figure 4.

The recurrence of bleeding was taken as event (1), whereas death or lost for followup was taken as censor (0) for 24 months of followup of all patients after the procedure.

Cumulative haemoptysis free survival rate among TB + Comorb group after BAE were 64.4%, 55.2% and 41.2% in 6, 12 and 24 months respectively; whereas in non-tuberculous disease it was 81.3%, 77.1% and 68.1% in 6, 12 and 24 months respectively. In tuberculosis alone without any risk factors it was 98.1%, 91.2% and 88.1% in 6, 12 and 24 months respectively. Table 4 shows cumulative haemoptysis control rates in all the three groups.

Disease free survival (DFS) as in our study haemoptysis recurrence free duration (RFD) analysis was done using Kaplan-Meier survival probability.

Group	6 Months	12 Months	24 Months
Tuberculosis alone	98.1%	91.2%	88.1%
TB + Comorb	64.4%	55.2%	41.2%
Non-TB	81.3%	77.1%	68.1%

Table 4. The Overall Cumulative Rate of Haemoptysis Recurrence Free Duration (RFD)

	Univariate (Mean) RFD ± SE (Days)	Log-Rank
TB Alone	1173.04	P<0.05
TB + Comorb	698.19	
Non-TB	878.01	

Table 5. Univariate Analysis of Haemoptysis Recurrence Free Duration

Characteristics	Multivariate Hazard Ratio	95% CI	P value
Smoking ≥ 30 pack-years	HR 2.157	1.243 - 4.581	<0.05
anticoagulant medications	HR 2.103	1.233 - 2.134	<0.05
Age ≥ 45 years	HR 2.192	1.335 - 3.846	<0.05

Table 6. Multivariate Analysis of Various Risk Factors on Haemoptysis Recurrence Free Duration

The Table 4 shows a statistical difference among the three groups ($P < 0.05$), especially in cases of TB + comorbid conditions where the recurrence of rebleeding were statistically higher than the rest of the group and univariate analysis shown in Table 5.

Secondary Outcome: Mortality Rate

Kaplan-Meier survival analysis was used to measure the univariate analysis of mortality among all the three groups. Mortality rate was significantly high in TB + Comorb group when compared to the rest of the groups ($p = 0.05$).

Analysis of parameters influencing on recurrent haemoptysis and mortality

The following parameters namely

1. Age ≥ 45 years
2. Smoking more ≥ 10 pack years (py).
3. Smoking more ≥ 20 pack years.
4. Smoking more ≥ 30 pack years.
5. Male gender.
6. Anti-coagulant medications were analysed.

Cox regression univariate analysis for these parameters were done for the calculation of recurrence-free rate and survival time. Among these parameters age ≥ 45 years, smoking ≥ 20 pack years, smoking ≥ 30 pack years, male gender and anticoagulant medications showed ($p < 0.05$) statistical difference. These parameters were checked with cox regression multivariate analysis.

In multivariate analysis smoking ≥ 30 pack-years (HR 2.157, 95% CI 1.243 - 4.581, $P = 0.003$), anticoagulant medications (HR 2.103, 95% CI 1.233 - 2.134, $P < 0.002$) were associated with recurrent haemoptysis, whereas age ≥ 45 years (HR 2.192, 95% CI 1.335 - 3.846, $P = 0.004$) was associated with mortality in multivariate analysis (Table 6).

Gender, smoking ≥ 10 pack years and smoking ≥ 20 pack years were not associated with any statistical significance in Cox regression multivariate analysis.

CONCLUSION

Prognosis of the TB patients without comorbid risk factors were good when compared to TB along with risk factors for BAE for massive haemoptysis. The risk factors namely diabetes mellitus (DM), human immunodeficiency virus (HIV), chronic liver diseases, chronic renal diseases and coronary artery diseases, not only play an important role in the activation of latent infection, but also causes increased mortality in these patients. So these risk factors namely pulmonary tuberculosis, diabetes mellitus, chronic liver disease, chronic renal diseases and HIV are the main

comorbidities in these patients increasing the risk of recurrent haemoptysis and mortality of patients undergoing BAE for massive haemoptysis.

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