



Aetiology, diagnosis and treatment of moderate-to-severe haemoptysis in a North American academic centre

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ABSTRACT Significant haemoptysis is a frightening event for patients and clinicians alike. There is a paucity of contemporary literature on the subject.

A retrospective analysis of hospitalisations for haemoptysis of more than 50 mL·day⁻¹ in a tertiary referral centre during a 5-year period was performed. Patient's characteristics, haemoptysis aetiology, management and outcome were individually recorded. The aim of this study was to detail the causes of moderate (50–200 mL·day⁻¹) to severe (>200 mL·day⁻¹) haemoptysis along with the diagnostic measures and treatment options used in their management in a 21st century, tertiary-care North American centre.

A total of 165 hospitalisations for moderate-to-severe haemoptysis were included in the analysis. Lung cancer (30.3%) and bronchiectasis (27.9%) proved to be most frequent aetiologies. Computed tomography (CT) imaging and bronchoscopy were complementary in identifying the source of bleeding. Bronchial artery embolisation (BAE) was the most common treatment approach (61.8%) and resulted in initial bleeding control in 73.5% of cases. In-hospital mortality was 13.9%, varying from 3.3% in the moderate group to 24.7% in the severe group. Despite being the favoured approach in patients with more severe bleeding, initial BAE therapy was associated with a trend towards lower mortality compared to initial non-BAE therapy.

In summary, lung cancer and bronchiectasis were the main causes of moderate-to-severe haemoptysis in our population, CT and bronchoscopy are complementary in identifying the source of bleeding, bleeding volume is associated with outcomes and BAE is a key management tool.

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In a contemporary North American population, lung cancer and bronchiectasis proved to be the leading causes of moderate-to-severe haemoptysis while CT and bronchoscopy appeared complementary in localising the source of bleeding <https://bit.ly/2BFLvOT>

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Introduction

Moderate-to-severe haemoptysis, although a rare event, is a cause of great concern for both patients and physicians [1]. Urgent care is required as haemoptysis is associated with high rates of morbidity and mortality [2, 3]. Previous studies have reported similar outcomes for moderate and severe haemoptysis [4].

Regarding the most frequent causes, there seems to be profound heterogeneity depending mainly on geographical location [5]. The aetiologies will also vary according to the severity of the haemoptysis. Tuberculosis (TB) has often been identified as one of the most common causes of significant haemoptysis in recent observational studies throughout the world [6]. However, this finding may not be accurate in some countries with higher socioeconomic levels [7]. Socioeconomic level may not be the only important factor as tuberculosis remains a frequent cause of significant haemoptysis in certain countries with a relatively high socioeconomic level [3, 8, 9]. Other frequent causes of moderate-to-severe haemoptysis reported are bronchiectasis, lung cancer, lower respiratory tract infections and mycetomas [6].

The value of different tests also remains unclear. Usually performed as the initial test, chest radiography identifies the location of bleeding in 45% to 65% of cases and leads to the identification of the cause of bleeding in as many as 35% of patients [10–13]. Whether a computed tomography (CT) scan or a bronchoscopy should be performed next depends on each individual case and if the patient's airway is secured. CHALUMEAU-LEMOINE *et al.* [14] showed in a prospective study that flexible bronchoscopy and CT scan performed equally to localise the origin of bleeding, but that CT scan more frequently led to a definitive diagnosis.

Treatment of moderate-to-severe haemoptysis can differ significantly depending on the cause, but bronchial artery embolisation (BAE) has shown its effectiveness in a wide variety of situations since being first described in 1974 [15]. Various new endoscopic techniques used to control further bleeding have also provided interesting results [6].

Mortality rates for severe haemoptysis are historically reported to be exceeding 50% when not managed aggressively [8]. In recent cohorts of severe haemoptysis in France [3] and Singapore [16], in-hospital mortality rates between 6% and 13% were observed.

Considering the paucity of literature on moderate-to-severe haemoptysis, especially in the current North American setting, we conducted a retrospective observational study at our tertiary pulmonary medicine referral centre. Our objective was to provide contemporary epidemiological, diagnostic and therapeutic information.

Methodology

We performed a retrospective observational study of inpatients with a diagnosis of haemoptysis at our tertiary referral institution, the Québec Heart and Lung Institute (Québec City, Canada). After obtaining approval from the institution research ethics board (approval no. 2017-2835), we identified all hospitalisations with a diagnosis of haemoptysis during a 5-year-period from September 2011 to September 2016.

Two investigators (SG and NQ) manually reviewed all the charts to confirm the diagnosis of haemoptysis and to identify the episodes of moderate-to-severe haemoptysis. Episodes were categorised as mild, moderate or severe haemoptysis. Haemoptysis of <50 mL per 24 h was classified as mild and patients were excluded. Haemoptysis of 50 to 200 mL per 24 h was classified as moderate and haemoptysis of >200 mL per 24 h was classified as severe. Although there is no volume threshold consensus in the literature, we chose 50 mL and 200 mL per 24 h to define moderate and severe haemoptysis based on experience from previous reports [17–20].

Population baseline characteristics were collected. The volume, onset and duration of haemoptysis were noted as reported in the patient's chart. The aetiologies of the haemoptysis were classified using the following groups: lung cancer, bronchiectasis (including cystic fibrosis (CF)-associated), lower respiratory tract infections, pulmonary embolism, iatrogenic, idiopathic and others. For each haemoptysis episode, we reviewed the care process, including all diagnostic/imaging tests performed regarding their timing and ability to localise the source of bleeding. Also, we recorded the modalities of treatment used and the order in which they were used. If BAE was performed, we noted any recurrence of bleeding after embolisation. Need for intensive care unit (ICU) admission, endotracheal intubation and in-hospital mortality were also documented. Descriptive statistics were used and univariate analyses were performed. Fisher's exact test was used to compare binary variables due to small sample size while a t-test was used to compare continuous variables with a normal distribution. Statistical analyses were verified by an independent statistician who used SAS statistical analysis software.

Results

A total of 560 hospitalisations with a diagnosis of haemoptysis were identified, 368 were excluded as they did not exceed 50 mL per 24 h, and 27 others were excluded as they were recurrences in a patient already included in the study. Hence, 165 hospitalisations for moderate-to-severe haemoptysis were identified from September 2011 to September 2016. Baseline characteristics of the studied patients are summarised in table 1. We identified 73 (44.2%) patients with severe haemoptysis and 92 (55.8%) with moderate haemoptysis. The overall median bleeding volume was 187 mL per 24 h. The most frequently encountered causes (table 2) were lung cancer (30.3%), followed by bronchiectasis (27.9%; non-CF=21.2%, CF=6.7%), lower respiratory tract infection (4.2%), pulmonary embolism (3.6%), iatrogenic (3.6%) and arteriovenous malformation (AVM) (3.0%). TB (1.2%) was rarely the aetiology of moderate-to-severe haemoptysis in our population. The leading causes in the moderate and severe groups were respectively bronchiectasis and lung cancer. Despite thorough investigation, 20% (n=33) of haemoptysis remained cryptogenic. In this subgroup, post-discharge follow-up after ≥ 1 year was available for 14 patients (42.4%) and led to a retrospective diagnosis in only three patients (one lung cancer, one heart failure and one iatrogenic secondary to multiple antiplatelet medications). Among the 14 patients, 3 had recurrence of haemoptysis within a year following discharge.

Chest radiography was the most performed diagnostic test (n=152, 92.1%) but led to localisation of bleeding source in only 13.8% of cases (21 of 152). Noncontrast CT imaging of the chest was obtained in 27 patients (16.4%), while contrast-enhanced CT was performed in 92 patients (55.8%). The bleeding localisation rates were 51.9% (14 of 27) and 52.2% (48 of 92), respectively. Flexible bronchoscopy, performed in 110 patients (65.5%), was the most effective at localising the source of bleeding (72 of 110, 65.5%). The source of haemoptysis remained unidentified in 27% (n=45) of cases, including in 6 patients

TABLE 1 Patient characteristics

Characteristics	Subjects
Patients n	165
Female sex	66 (40.0%)
Age years mean	62.8
Smoking	117 (70.9%)
Active	43 (26.1%)
Pack-years mean [#]	38.3
Prior episode(s) of haemoptysis	38 (23.0%)
Comorbidities	
COPD	47 (28.5%)
Bronchiectasis	42 (25.5%)
Cystic fibrosis	13 (7.9%)
Pulmonary hypertension	7 (4.2%)
Atrial fibrillation	24 (14.5%)
Cardiac ischaemic disease	40 (24.2%)
Heart failure	15 (9.1%)
Thromboembolic disease	6 (3.6%)
Lung cancer	
Past lung cancer	13 (7.9%)
Active lung cancer	42 (25.5%)
Known endobronchial lesion	19 (11.5%)
Medication	
ASA	57 (34.5%)
Clopidogrel	7 (4.2%)
ASA and clopidogrel	5 (3.0%)
Oral anticoagulant	
Apixaban/rivaroxaban/dabigatran	8 (4.8%)
Warfarin	20 (12.1%)
INR mean	2.56
LMWH (therapeutic dosage)	7 (4.2%)
Intravenous heparin	5 (3.0%)
ASA+one anticoagulant	10 (6.1%)

Data are presented as n (%), unless otherwise stated. ASA: acetylsalicylic acid; INR: international normalised ratio; LMWH: low molecular weight heparin. [#]: including both active and former smokers.

TABLE 2 Haemoptysis and aetiologies

	Moderate	Severe	Total
Patients	92 (55.8%)	73 (44.2%)	165 (100%)
Aetiologies			
Lung cancer	20 (21.7%)	30 (41.7%)	50 (30.3%)
Bronchiectasis	24 (26.1%)	11 (15.1%)	35 (21.2%)
Idiopathic	21 (22.8%)	12 (16.4%)	33 (20.0%)
Cystic fibrosis-related bronchiectasis	5 (5.4%)	6 (8.2%)	11 (6.7%)
Lower respiratory tract infection	5 (5.4%)	2 (2.8%)	7 (4.2%)
Iatrogenic	5 (5.4%)	1 (1.4%)	6 (3.6%)
Pulmonary embolism	4 (4.4%)	2 (2.8%)	6 (3.6%)
Others			
Arteriovenous malformation	2 (2.2%)	3 (4.1%)	5 (3.0%)
Pulmonary oedema	2 (2.2%)	1 (1.4%)	3 (1.8%)
Aspergilloma	1 (1.1%)	1 (1.4%)	2 (1.2%)
Tuberculosis	1 (1.1%)	1 (1.4%)	2 (1.2%)
Vasculitis	1 (1.1%)	0	1 (0.6%)
Arterio-bronchial fistula	0	1 (1.4%)	1 (0.6%)
Granulomatous disease	0	1 (1.4%)	1 (0.6%)
Lymphoma	0	1 (1.4%)	1 (0.6%)
Pulmonary hypertension	1 (1.1%)	0	1 (0.6%)
Median volume in 24 h mL	98	316	187
Duration of active haemoptysis			
<8 h	12 (13.0%)	18 (24.7%)	30 (18.2%)
8–24 h	20 (21.7%)	25 (34.2%)	45 (27.3%)
24–48 h	18 (19.6%)	9 (12.3%)	27 (16.4%)
>48 h	42 (45.7%)	21 (28.9%)	63 (38.2%)

who decided to receive palliative care prior to completing investigations. Two patients died from uncontrolled bleeding prior to completing investigations.

Bleeding source was localised in 13 of 24 (54.2%) patients who underwent CT imaging (including contrast-enhanced) without bronchoscopy and in 19 of 21 patients (90.5%) in whom bronchoscopy was performed without additional CT scan. Eighty-nine patients underwent both CT imaging and bronchoscopy (figure 1). Among the 71 patients in whom the CT was carried out first, localisation of bleeding was established in 42 cases (59%). Among the 29 patients in whom the CT performed first failed to localise the bleeding, bronchoscopy succeeded in 13 (45%). Among the 18 patients in whom bronchoscopy was performed before CT, the bleeding source was identified in 13 (72%). In the five patients in whom bleeding source remained unknown after bronchoscopy, CT imaging localised bleeding source in three cases (60%).

BAE was the most common treatment approach (n=102 (61.8%)) (figure 2). Eighty-seven patients were oriented towards BAE as an initial therapy and 15 others received it after other modalities failed. Surgery (five patients, 3%) was only rarely used. Eight patients (4.8%) had therapeutic bronchoscopy to control the haemoptysis. Seventy-four patients initially had a noninvasive observation approach (figure 3). Among them, 28 received antibiotics and 20 had their antiplatelet or anticoagulant medication stopped. Fifteen patients eventually needed rescue BAE after the initial approach failed, including 11 patients in the antibiotics subgroup and 3 patients in the antiplatelet or anticoagulation cessation subgroup. Thirteen patients died, 6 after a decision of palliative care was made, 5 of uncontrolled haemoptysis (including 1 after a failed BAE) and 2 from other causes.

Despite being the favoured approach (table 3) in patients with higher mean bleeding rate (206.8 mL per 24 h *versus* 163.3 mL per 24 h), initial BAE therapy was associated with a trend towards lower mortality compared to initial non-BAE therapy (11.5% *versus* 17.9%, $p=0.27$). However, in the initial non-BAE therapy group, four patients were oriented to palliative care upon admission and eventually died during their hospitalisation. If we exclude these 4 patients, mortality in the initial non-BAE therapy group is 13.5% (10 of 74).

Haemoptysis recurrence rate prior to discharge after BAE was 26.5% (27 of 102). Of those 27 patients, 10 (37.0%) underwent a second BAE. A second BAE stopped the haemoptysis in all but two patients, who eventually died of uncontrolled bleeding. Among the 17 patients who did not have a second BAE,

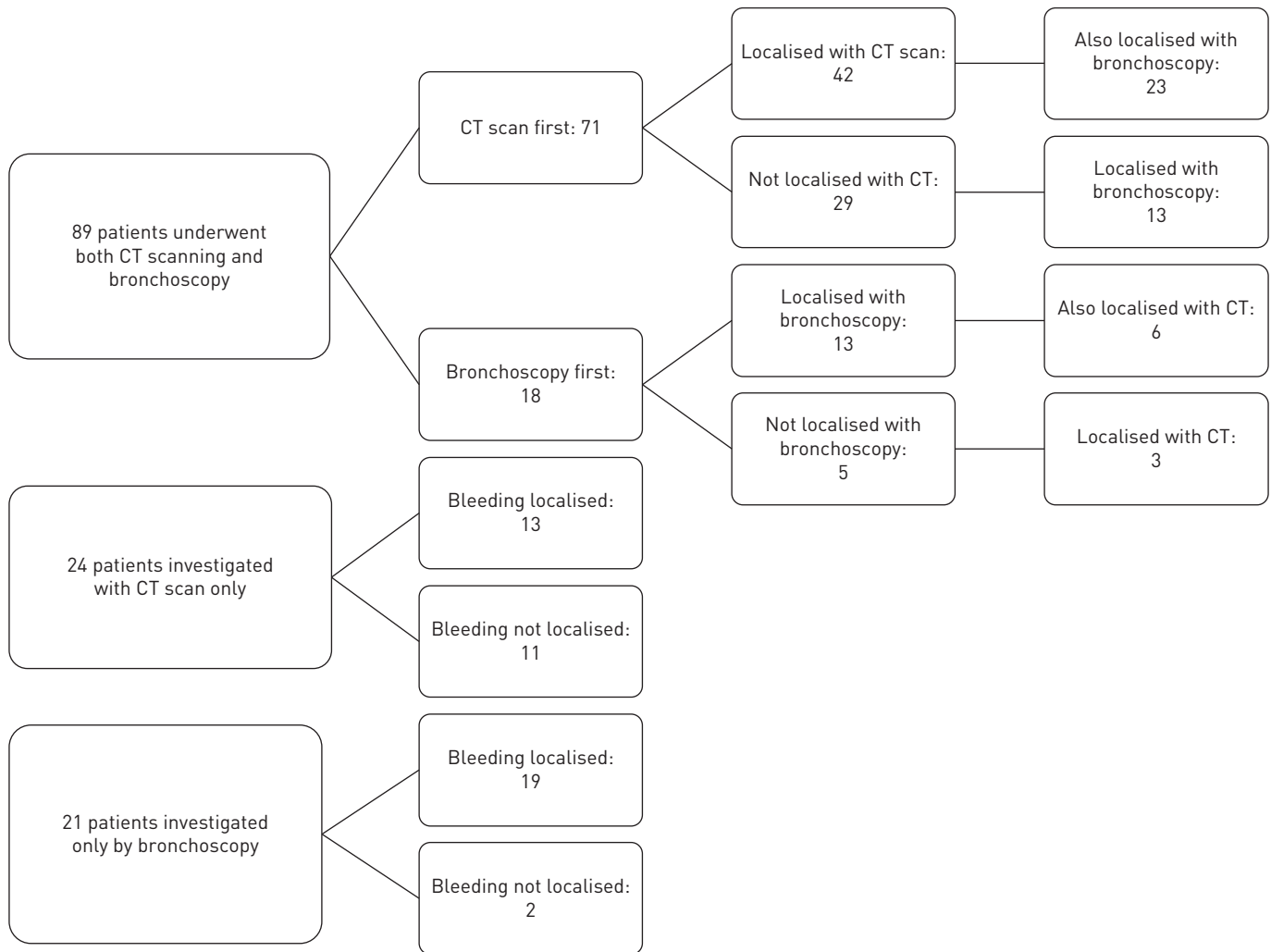


FIGURE 1 Bleeding localisation of bronchoscopy and computed tomography (CT).

observation alone led to bleeding cessation in 11, 3 died of uncontrolled bleeding, 2 opted for palliative care and 1 had endoscopic control of the haemoptysis.

The average length of hospital stay was 9.1 days. A total of 62 patients (38%) were admitted to the ICU, where the mean stay was 3.2 days. Twenty-four individuals (14%) were intubated and mechanically ventilated. The in-hospital mortality rate was 13.9% (n=23), mostly after changes in goals of care (n=11, 47.8%) and uncontrolled haemoptysis (n=6, 26.0%). Among those whose goals of care were changed, six opted for palliative care when faced with the underlying progression of their cancer and associated comorbidities and five patients were transferred to a palliative care unit after treatments failed to control the bleeding. Lung cancer (12 of 23, 52.2%) was the most frequent aetiology leading to death during the hospitalisation and mortality rate was higher when lung cancer was the underlying aetiology (24.0% (12 of 50) *versus* 7.7% (11 of 142) for other causes).

Severe haemoptysis was associated with poor outcomes (table 4). The mean length of hospital stay was not statistically significantly longer (10.0 *versus* 8.4 days, p=0.47). However, ICU stay (57.5% *versus* 21.7%, p<0.001) and endotracheal intubation (29.2% *versus* 3.3%, p<0.001) were more likely to be needed. In-hospital mortality rate was also higher in those with severe haemoptysis (27.4% *versus* 3.3%, p<0.001).

Discussion

In this observational, retrospective study of cases of moderate and severe haemoptysis presenting to our referral centre, we identified causes of significant haemoptysis that were somewhat different from what is currently shown in various cohorts around the globe. To our knowledge, this is the largest modern moderate-to-severe haemoptysis cohort in a tertiary North American setting. In opposition to previous

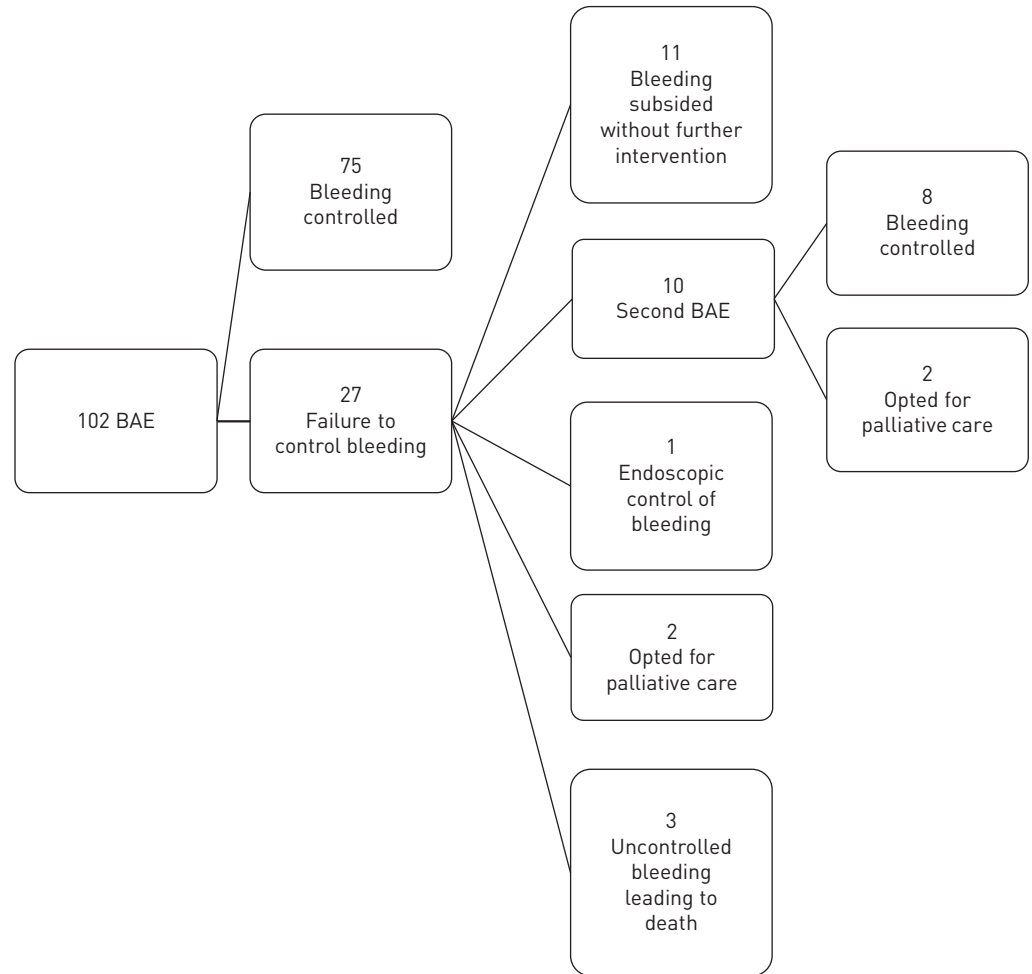


FIGURE 2 Outcomes of patients undergoing bronchial artery embolisation (BAE).

reports, including some from France [5, 8, 11], Austria [21] and the USA [7] in the years 2000–2010, TB was an uncommon cause of significant haemoptysis in our population; however, this lower rate of tuberculosis is to be interpreted in the context of the low prevalence of the disease in our catchment area. Lung cancer was the leading cause of significant haemoptysis in our cohort, especially in severe bleeding of more than 200 mL per 24 h (41.7% of these cases). The proportion of lung cancer differs from other studies in higher socioeconomic settings where bronchiectasis was at the forefront and lung cancer was a less frequent aetiology, except in one series by VALIPOUR *et al.* [21] from Austria (35% of lung cancer in haemoptysis of >150 mL). Furthermore, lung cancer was also the aetiology associated with the highest mortality rate of (24.0% versus 7.7% for other causes). In both groups (moderate and severe), lung cancer, bronchiectasis and idiopathic were the most frequent diagnoses. The relatively significant number of cases due to CF-associated bronchiectasis is probably specific to our population and imputable to a reference bias at our institution which is the referral CF centre of a 2 million people catchment area with a relatively high prevalence of CF due to local genetic factors. A high proportion of haemoptysis remained of unknown aetiology (20%) despite thorough investigation which is consistent with previous publications. ABDULMALAK *et al.* [5] extracted data from the French nationwide database over 5 years (2008–2012) and analysed 75 000 cases of haemoptysis (mild to severe). A total of 50% of cases were cryptogenic. In more severe haemoptysis, KIRAL *et al.* [22] identified 22% of idiopathic cases in 203 Turkish patients with haemoptysis of >200 mL per 24 h. FARTOUKH *et al.* [8] in France noted 18% of cryptogenic haemoptysis in their series of 1087 patients necessitating ICU admission.

In our series, flexible bronchoscopy was globally slightly superior to CT at localising the source of bleeding (65.5% versus 52.0%). Patients initial characteristics did not differ significantly between those who had bronchoscopy or CT first except that more patients initially undergoing flexible bronchoscopy had previously been intubated. The sequence of exam seems to have been frequently dictated by their

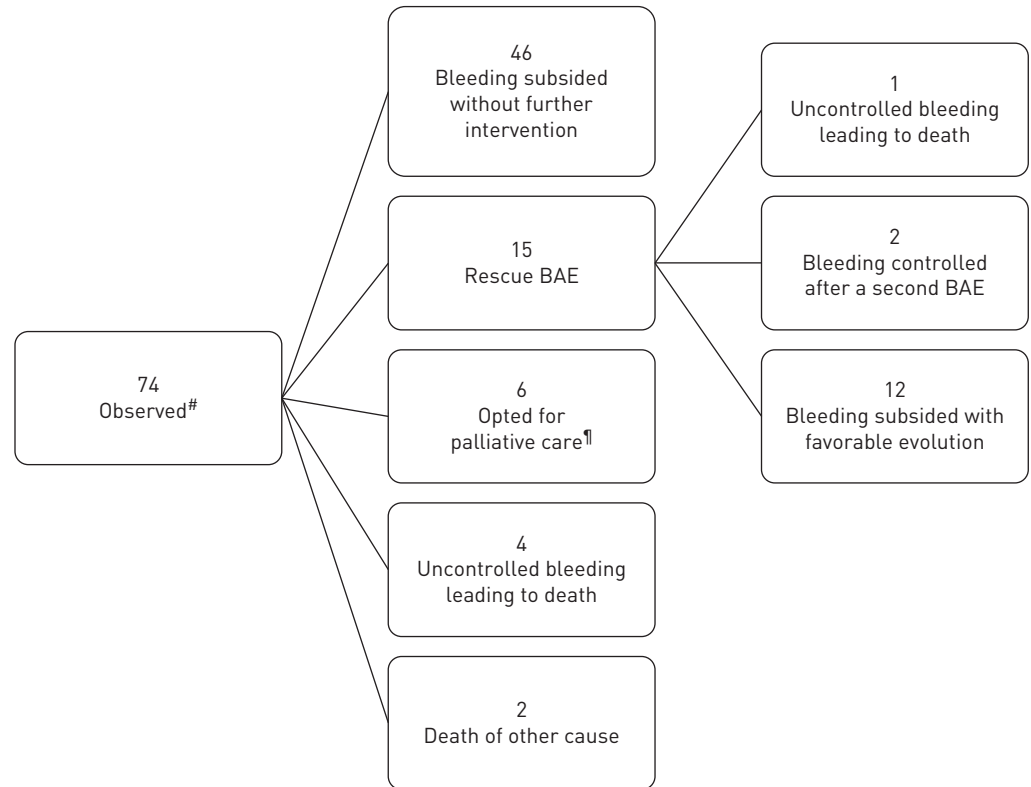


FIGURE 3 Outcomes of patients who were treated with a noninvasive observational approach. BAE: bronchial artery embolisation. #: amongst observed patients, 28 were on antibiotics and 20 had their antiplatelets and/or anticoagulation stopped; ¶: six patients opted for palliative care with ongoing bleeding.

	Initial BAE strategy	Initial non-BAE strategy#
Patients	87 (52.7%)	78 (47.3%)¶
Age years mean	64.2	61.1
Female sex	31 (35.6%)	35 (44.9%)
Volume of haemoptysis mL per 24 h mean	206.8	163.3
Severe haemoptysis	47 (54.0%)	26 (33.3%)
Length of hospital stay days mean	9.6	8.6
ICU	40 (46.0%)	22 (28.2%)
Endotracheal intubation	15 (17.2%)	9 (11.5%)
In-hospital mortality	10 (11.5%)	14 (17.9%)
Aetiologies		
Lung cancer	27 (31.0%)	23 (29.5%)
Bronchiectasis	17 (19.5%)	18 (23.1%)
Idiopathic	23 (26.4%)	10 (12.8%)
Cystic fibrosis-related bronchiectasis	5 (5.7%)	6 (7.7%)
Lower respiratory tract infection	1 (1.1%)	6 (7.7%)
Iatrogenic	3 (3.4%)	3 (3.8%)
Pulmonary embolism	1 (1.1%)	5 (6.4%)
Arteriovenous malformation	4 (4.6%)	1 (1.3%)
Pulmonary oedema	0	3 (3.8%)
Others	6 (6.9%)	3 (3.8%)

ICU: intensive care unit. #: 15 patients initially assigned to non-BAE approach later received BAE. Eight had bronchiectasis (including one CF-related), four had lung cancer, one had iatrogenic haemoptysis, one had arteriovenous malformation and the other case remained idiopathic; ¶: four of those patients had surgery.

TABLE 4 Outcomes and mortality

	Total (n=165)	Moderate (n=92)	Severe (n=73)
Number of days in hospital mean	9.1	8.4	10.0
ICU admission	62 (38%)	20 (21.7%)	42 (57.5%)
Number of days in ICU median	3.2	3.5	3.0
Endotracheal intubation	24 (14.5%)	3 (3.3%)	21 (29.2%)
In-hospital mortality	23 (13.9%)	3 (3.3%)	20 (27.4%)

ICU: intensive care unit.

availability as a CT had been ordered and was pending in the vast majority of patients undergoing bronchoscopy first. Adding bronchoscopy after CT and CT after bronchoscopy both seem to have added localisation value. Based on our data, we cannot recommend one localising exam over the other, but we believe that both exams are complementary. CT scanning is the exam of choice for all noncentral lesions and for identifying bronchiectasis, peripheral lung cancer, pulmonary embolism, arteriovenous malformation and aspergillomas [23]. On the other hand, bronchoscopy is valuable for more central or endobronchial lesions, where it may allow concurrent identification, histopathological diagnosis and therapeutic measures on a specific bleeding site. We recommend, based on our experience, a contrast-enhanced CT with a dedicated arterial phase first if the patient is stable enough to be sent to radiology. This will provide localisation information in a significant proportion of patients, clarify anatomy and define bronchial or pulmonary vasculature origin for BAE if it is deemed necessary. If, after the CT, the bleeding source remains unidentified, we believe flexible bronchoscopy, if clinically judged safe, has an interesting additional value. It is important to understand that we focused on localisation rate, but exams also have a diagnostic rate which was felt to be too difficult to evaluate retrospectively as CT is often suggestive but not diagnostic.

The safety of a flexible bronchoscopy in patients presenting significant haemoptysis is of the utmost importance. While no specific criteria defining safety other than clinician judgment was highlighted by this retrospective study, we believe that bronchoscopy should not be performed in an actively bleeding patient unless a plan and appropriate material are prepared for eventual endotracheal intubation. Furthermore, endobronchial therapies to intervene on the source of bleeding such as cold saline, adrenaline or tranexamic acid should be readily available. Ideally, CT scanning should be performed first (if the patient is stable enough to be sent to the radiology department) and bronchoscopy kept for later as the patient's condition stabilises and CT images allow for guidance of the endoscopic technique. Bronchoscopy under general anaesthesia may be necessary when high volume active bleeding and hypoxaemia are concerns. Rigid bronchoscopy can be useful in this population by stabilising the airway, providing the possibility to use large bore suction and allowing endoscopic interventions such as the use of laser or argon and the positioning of oxidised regenerated cellulose [21], biocompatible glue [24], endobronchial stents [25] or silicone spigots [26, 27].

Regarding treatment options, BAE was the main treatment used in moderate-to-severe haemoptysis and achieved a relatively high bleeding control rate. It is interesting to note that there was a trend towards lower mortality with initial BAE approach, despite being the favoured therapy for more severe bleeding.

When designing this study, we chose thresholds of 50 and 200 mL per 24 h for moderate and severe haemoptysis based on reports from previous studies [17–20]. As mentioned earlier, aetiologies were globally similar between the two groups, but outcomes were different. Severe haemoptysis was associated with a higher mortality rate and a greater need for endotracheal intubation and ICU. The overall in-hospital mortality rate of 13.9% is higher than the 6.5% reported by FARTOUKH *et al.* [3] in 1087 patients who needed ICU admission in France. The mortality rate of 27.4% in severe cases is also much higher than the 12.9% rate reported by ONG and ENG [16] in a population from Singapore with haemoptysis of >300 mL·day⁻¹ or necessitating intubation. The higher proportion of patients with lung cancer most likely account for the difference (lung cancer was the aetiology in 17% [3] and 7% [16] of patients in the previously mentioned studies). Had we chosen different thresholds for moderate and severe haemoptysis; mortality rates would not have been dramatically different. Had we opted to identify severe bleeding as 100, 150, 200, 250 or 350 mL·day⁻¹, mortality rates would have respectively been 16.7% (21 of 126), 24.7% (21 of 85), 27.4% (20 of 73), 30.8% (20 of 65) and 37.5% (15 of 40) for the severe group and 5.1% (2 of 39), 2.5% (2 of 80), 3.3% (3 of 92), 3% (3 of 100) and 6.4% (8 of 125) for the moderate group.

Our study has several limitations. The retrospective design limited the possibility to analyse different therapeutic approaches as more aggressive therapies may have been limited in patients with a poor prognosis due to their underlying disease. Haemoptysis volume and duration may also not have been recorded accurately. While reviewing the charts, we relied on written information about the volume of haemoptysis. No specific measurement tool was routinely used although nursing staff in our institution are instructed to objectively measure haemoptysis in a graded sputum collection container in cases that were moderate to severe. We are aware quantifying moderate-to-severe haemoptysis in the acute scenario can be challenging. Therefore, all reported quantities may not be perfectly accurate, and the presence of recall bias is likely. Our study only analysed data from a single centre which may have induced a selection and reference bias. Finally, the cohort of patients studied is also relatively small, but it was nevertheless larger than other studies of significant haemoptysis, which had fewer than 100 patients [9–22, 28, 29].

Conclusion

In conclusion, lung cancer and bronchiectasis were the leading causes of moderate-to-severe haemoptysis in our contemporary North American population. CT and bronchoscopy are complementary to localise the source of bleeding. BAE is effective in the majority of cases at controlling haemoptysis. Haemoptysis of 50–200 mL was associated with a significantly better outcome than haemoptysis >200 mL.

Conflict of interest: None declared.

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