Long-term Prognostic Outcomes in Patients With Hemoptysis

Michele Mondoni (✉ michele.mondoni@asst-santipaolocarlo.it)

Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan

Paolo Carlucci

Respiratory Unit, Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano

Giuseppe Cipolla

UOC Pneumologia, ASST Lodi

Matteo Pagani

UO Pneumologia ed endoscopia toracica, Azienda Ospedaliero Universitaria di Parma

Francesco Tursi

UOS Servizio Pneumologia, Ospedale di Codogno, ASST Lodi

Alessandro Fois

Lung Disease Unit, Dept of Clinical and Experimental Medicine, University of Sassari

Pietro Pirina

Lung Disease Unit, Dept of Clinical and Experimental Medicine, University of Sassari

Sara Canu

Lung Disease Unit, Dept of Clinical and Experimental Medicine, University of Sassari

Stefano Gasparini

Pulmonary Disease Unit, Department of Internal Medicine, Azienda Ospedali Riuniti, Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Ancona

Martina Bonifazi

Lung Disease Unit, Dept of Clinical and Experimental Medicine, Azienda Ospedali Riuniti, Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Ancona

Silvia Marani

UO Medicina Interna, AUSL Modena, Ospedale di Carpi (MO)

Andrea Claudio Comel

UO Pneumologia, Ospedale P. Pederzoli, Peschiera del Garda (VR)

Laura Saderi

Clinical Epidemiology and Medical Statistics Unit, Dept of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari

Sabrina De Pascalis

Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan

Fausta Alfano

Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan

Stefano Centanni

Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan

Giovanni Sotgiu

Clinical Epidemiology and Medical Statistics Unit, Dept of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari

---

Research Article

Keywords: hemoptysis, recurrence, lung cancer, bronchoscopy, anticoagulant, antiplatelet, mortality, bronchiectasis

Posted Date: April 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-426332/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Respiratory Research on August 4th, 2021. See the published version at <https://doi.org/10.1186/s12931-021-01809-6>.

Abstract

Background: Hemoptysis is a challenging symptom which can be associated with potentially life-threatening medical conditions. Follow-up is key in these patients to early detect new or misdiagnosed pathologic findings. Few prospective studies evaluated long-term prognostic outcomes. Furthermore, the role played by antiplatelet and anticoagulant drugs on mortality and recurrence rates is unclear.

The aim of the study was to assess the mortality after 18 months of follow-up; furthermore, it was evaluated the incidence of recurrences and the factors associated with both recurrence and death (including the role played by anticoagulant and antiplatelet drugs).

Methods: Observational, prospective, multicentre, Italian study.

Results: 451/606 (74.4%) recruited patients with hemoptysis completed the 18 months follow-up.

22/604 (3.6%) diagnoses changed from baseline to the end of the follow-up. 83/604 (13.7%) patients died. In 52/83 (62.7%) patients, death was the outcome of the disease which caused hemoptysis at baseline. Only the diagnosis of lung neoplasm was associated with death (OR (95%CI): 38.2 (4.2-347.5); p-value: 0.0001).

166 recurrences were recorded in 103/604 (17%) patients. The diagnosis of bronchiectasis was significantly associated with the occurrence of a recurrence (OR (95% CI): 2.6 (1.5-4.3)); p-value <0.0001).

Anticoagulant, antiaggregant, and anticoagulant plus antiaggregant drugs were not associated with an increased risk of death and recurrence.

Conclusions: Our study showed a low mortality rate in patients with hemoptysis followed-up for 18 months. Pulmonary malignancy is the main etiology and the main predictor of death, whereas bronchiectasis is the most frequent diagnosis associated with recurrence. Antiplatelet and/or anticoagulant therapy do not change the risk of death or recurrence. Follow-up is recommended in patients initially diagnosed with lower airways infections and idiopathic bleedings.

Clinical trial registration: NCT02045394.

Background

Hemoptysis is a challenging symptom which can be associated with potentially life-threatening medical conditions^{1,2}. Recent studies showed that lung cancer, bronchiectasis, and lower respiratory tract infections are the most frequent etiologies²⁻⁸. However, despite an accurate initial work-up, a subgroup of patients with hemoptysis does not have an etiological diagnosis (*i.e.*, idiopathic or cryptogenic hemoptysis)²⁻⁹; furthermore, diagnostic changes from the baseline assessment to recurrences were recently described^{2,9}. In particular, lung cancer was found in patients with idiopathic hemoptysis or lower

respiratory infections and a diagnosis of bronchiectasis was performed in a non-negligible proportion of patients initially diagnosed with cryptogenic bleeding^{2,10}.

In this context, follow-up is key to detect new or misdiagnosed pathologic findings (*e.g.*, lung malignancy)^{2,6,8}.

Several factors might influence the long-term prognostic outcomes of patients with hemoptysis. Few prospective studies evaluated their survival rate, the mortality-related risk factors, as well as the incidence of recurrence and its associated variables^{7,8}. Furthermore, the role played by antiplatelet and anticoagulant drugs is still unclear.

The primary aim of this study was to assess the mortality after 18 months of follow-up; furthermore, the incidence of recurrences and the clinical factors associated with recurrence and mortality were evaluated. The role of anticoagulant and antiplatelet drugs on these outcomes was also studied.

Materials And Methods

Study design

This is a secondary analysis of an observational, prospective, multicentre, Italian study aimed at evaluating the epidemiology of hemoptysis in Italy and the diagnostic yield of the most frequently prescribed diagnostic techniques⁵. It was approved by the ethical committees of five Italian participating hospitals and registered at ClinicalTrials.gov (identifier: NCT02045394). Written informed consent was signed by all recruited patients⁵, who were followed-up for 18 months.

One month after the recruitment and the first initial assessment, a hospital clinical re-evaluation was scheduled. After three, six, nine, twelve, and eighteen months a phone call was planned for every patient. At each follow-up visit information on occurrence, timing, and severity of recurrences was collected.

In case of recurrence a new clinical assessment was performed; data on clinical, radiological, endoscopic examinations, as well as on symptom management were recorded.

Patients and interventions

From July 2013 to September 2015, adult (*i.e.*, ≥ 18 years old) patients with haemoptysis requiring an etiological diagnosis were considered eligible for recruitment⁵ and consecutively enrolled. Exclusion criteria were the following: 1) etiology of haemoptysis already known; 2) refusal to sign the informed consent.

The follow-up period lasted from December 2015 to February 2018.

Severity of haemoptysis was graded by the first attending physician. Patients were divided into three groups based on the total amount of blood expectorated in 24 hours (h)^{5,7}: mild (*i.e.*, drops of blood to 20

millilitres (ml)/24 h), moderate (*i.e.*, 20–500 ml/24 h), severe (*i.e.*, > 500 ml/24 h).

Outcome measures

The primary outcome was the survival rate of patients with hemoptysis. Furthermore, it was calculated the incidence of recurrence and the main factors associated with recurrence and the mortality. The effectiveness of antiplatelet and anticoagulant drugs on these outcomes was specifically investigated.

Changes in the diagnosis of hemoptysis from baseline to the end of follow-up were recorded.

Statistical analysis

Qualitative and quantitative variables were collected with an ad hoc electronic form. Qualitative variables were described with absolute and relative (percentage) frequencies, whereas quantitative variables were summarized with medians (interquartile ranges, IQR) for their non-parametric distribution. Univariate and multivariate logistic regression analysis was performed to assess the relationship between clinical, demographic, and epidemiological variables and the outcomes death and recurrence. A two-tailed p-value less than 0.05 was considered statistically significant. All the statistical computations were performed with the statistical software STATA version 16 (StatsCorp, Texas, USA).

Results

451 out of 606 (74.4%) patients who were recruited⁵ completed the 18 months' follow-up.

The initial etiological diagnoses were previously described⁵.

In addition to specific etiological therapy, bronchial artery embolization was performed in 13/606 (2.1%) patients, bronchoscopy was performed with a therapeutic aim (e.g., administration of topical vasoconstriction, Fogarty balloon, endobronchial argon plasma coagulation and laser therapy) in 99/604 (16.4%) patients. Oral and intravenous tranexamic acid were prescribed in 119/606 (19.6%) patients.

70/606 (11.5%) patients were lost to follow-up, whereas 83/606 (13.7%) died during the study-period. 15/83 (18.1%) patients died within one month after the enrollment, 21/83 (25.3%) between the first and the third month of follow-up, 14/83 (16.9%) between the third and the sixth month, 26/83 (31.3%) between the sixth and the twelfth month, and 7/83 (8.4%) between the twelfth and the eighteenth month.

In 52/83 (62.7%) patients, death was the outcome of the disease which caused hemoptysis at baseline: 42 died for lung cancer (eight during a recurrence), seven patients for metastatic pulmonary malignancy, two patients for pneumonia, and one for a bronchiectasis exacerbation. One patient, initially diagnosed with idiopathic hemoptysis, died during a recurrence without an identifiable cause of bleeding.

In the univariate analysis, age > 70 years (odds ratio, OR, (95%CI): 9.5 (1.3–70.5); p-value: 0.03), being male (OR (95%CI): 2.3 (1.3–4.1); p-value: 0.005), moderate hemoptysis (OR (95%CI): 1.9 (1.2–3.0), p-value: 0.01), smoking history (≥ 10 pack/years: OR (95%CI): 3.5 (1.8–6.7); p-value: <0.0001; ≥ 30

pack/years: 1.9 (1.1–3.4)); p-values: 0.02), and pulmonary malignancy (OR (95%CI): 15.6 (9.2–26.5); p-value: <0.0001) were associated with an increased risk of mortality. In the multivariate analysis only the diagnosis of lung neoplasm resulted significantly associated with the above-mentioned outcome (OR (95%CI): 38.2 (4.2-347.5); p-value: 0.0001) (Table 1).

Table 1
Demographic and clinical variables predictive of mortality in patients with hemoptysis

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age (classes)	< 40 years	Ref.	Ref.		
	40–54 years	0.8 (0.1–9.0)	0.85		
	55–70 years	3.3 (0.4–26.4)	0.25		
	> 70 years	9.5 (1.3–70.5)	0.03	5.0 (0.8–32.7)	0.10
Sex male		2.3 (1.3–4.1)	0.005	1.3 (0.2–7.4)	0.76
Hemoptysis severity	Mild	Ref.	Ref.		
	Moderate	1.9 (1.2–3.0)	0.01		
	Severe	0.6 (0.1–4.6)	0.61		
Smoking history	≥ 10 pack/years	3.5 (1.8–6.7)	< 0.0001	0.5 (0.1–3.5)	0.46
	≥ 30 pack/years	1.9 (1.1–3.4)	0.02		
Number of recurrences		0.2 (0.1–0.7)	0.009	0.6 (0.2–2.3)	0.46
Severity of recurrences	Mild	Ref.	Ref.		
	Moderate	3.6 (1.2–10.8)	0.02		
	Severe	10.8 (1.6–73.9)	0.02		
Antiplatelet therapy		1.3 (0.8–2.1)	0.37		
Anticoagulant therapy		1.5 (0.8–2.9)	0.25		
Antiplatelet + anticoagulant therapy		1.3 (0.8–2.1)	0.24		
Pneumonia/lung abscess		0.7 (0.3–1.3)	0.20		
Malignancy (primary and metastatic)		15.6 (9.2–26.5)	< 0.0001	38.2 (4.2–347.5)	0.0001
Bronchiectasis		0.1 (0.0–0.5)	0.004	0.3 (0.0–3.7)	0.37
Acute bronchitis		-	-		
Cryptogenic hemoptysis		0.3 (0.1–1.1)	0.08		

22/606 (3.6%) diagnoses changed from baseline to the end of the follow-up (Table 2). In particular, pulmonary malignancy was described in four cases initially diagnosed with idiopathic bleedings, in two patients with an exacerbation of chronic obstructive pulmonary disease (COPD) (both with a smoking history > 20 pack/years), and in four patients with pneumonia/lung abscess (two of them active smokers). In 7/22 (32%) patients the new diagnosis was performed during a recurrence: lung cancer was described in two patients with an initial diagnosis of pneumonia/lung abscess and in one with an idiopathic bleeding. In two patients an upper airways lesion was found after an initial diagnosis of acute bronchitis and idiopathic bleedings. An upper digestive hemorrhage and a pulmonary embolism were diagnosed in two patients initially diagnosed with cryptogenic hemoptysis and pneumonia, respectively.

Table 2
Variation in the diagnosis from the initial assessment after 18 months follow-up

Initial diagnosis	Diagnosis at the end of the follow-up	Patients number
Pneumonia/lung abscess	Lung cancer	4
Pneumonia/lung abscess	Pulmonary embolism (with infarction)	2
Pneumonia/lung abscess	Bronchiectasis	1
Cryptogenic hemoptysis	Lung cancer	4
Cryptogenic hemoptysis	Upper airways bleeding disease	1
Cryptogenic hemoptysis	ILD	1
Cryptogenic hemoptysis	Hematemesis	1
COPD exacerbation	Bronchiectasis	2
COPD exacerbation	Pulmonary malignancy	1
COPD exacerbation	Lung cancer	1
Acute bronchitis	Bronchiectasis	1
Acute bronchitis	COPD exacerbation	1
Acute bronchitis	Upper airways bleeding disease	1
Acute bronchitis	ILD	1
COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease		

166 recurrences were recorded in 103/606 (17%) patients (Table 3). The median (IQR) number of events was 1 (1–2). Recurrences were recorded in 28/103 (27.2%) patients with bronchiectasis (45 bleeding events), in 24/103 (23.3%) with pulmonary malignancy (22/103 (21.4%) with lung cancer (26 events) and 2/103 (1.9%) with pulmonary metastasis (4 events), in 13/103 (12.6%) with pneumonia/lung abscess (21 events). Bronchiectasis and pneumonia/lung abscess related recurrences were mostly mild (20 (71.4%)

and 13 (100%) patients, respectively), whereas in case of lung cancer mild to moderate bleedings were found in 10 (45.5%) patients. 2 (7.1%) severe recurrences were recorded in patients with both bronchiectasis and lung cancer.

Table 3
Hemoptysis recurrences and their severity in 103 patients related to the final diagnosis

Final diagnosis	Events	Patients	Mild	Moderate	Severe
Bronchiectasis, n (%)	45	28 (27.2)	20 (71.4)	6 (21.4)	2 (7.1)
Pulmonary malignancy, n (%)	30	24 (23.3)	11(36.6)	11 (36.6)	2 (0.8)
Lung cancer, n (%)	26	22 (21.4)	10 (45.5)	10 (45.5)	2 (9.1)
Pulmonary metastasis, n (%)	4	2 (1.9)	1 (50.0)	1 (50.0)	0 (0.0)
Pneumonia/lung abscess, n (%)	21	13 (12.6)	13 (100)	0 (0.0)	0 (0.0)
COPD (exacerbation), n (%)	13	7 (6.8)	7 (100.0)	0 (0.0)	0 (0.0)
Acute bronchitis, n (%)	11	7 (6.8)	7 (100.0)	0 (0.0)	0 (0.0)
Cryptogenic hemoptysis, n (%)	10	6 (5.8)	5 (83.3)	1 (16.7)	0 (0.0)
Upper airways bleeding disease, n (%)	8	4 (3.9)	2 (50.0)	2 (50.0)	0 (0.0)
Post-tuberculosis sequelae, n (%)	8	3 (2.9)	2 (66.7)	1 (33.3)	0 (0.0)
Other pulmonary/bronchial vascular lesion, n (%)	5	2 (1.9)	1 (50.0)	0 (0.0)	1 (50.0)
Pulmonary embolism, n (%)	5	2 (1.9)	1 (50.0)	1 (50.0)	0 (0.0)
Atypical mycobacteriosis, n (%)	2	1 (1.0)	1 (100.0)	0 (0.0)	0 (0.0)
Active tuberculosis, n (%)	2	2 (1.9)	1 (50.0)	1 (50.0)	0 (0.0)
Iatrogenic or traumatic, n (%)	2	1 (1.0)	1 (100.0)	0 (0.0)	0 (0.0)
Tracheal granuloma, n (%)	2	1 (1.0)	1 (100.0)	0 (0.0)	0 (0.0)
Hematemesis, n (%)	1	1 (1.0)	0 (0.0)	1 (100.0)	0 (0.0)
Interstitial lung disease, n (%)	1	1 (1.0)	1 (100.0)	0 (0.0)	0 (0.0)
COPD: chronic obstructive pulmonary disease					

The univariate analysis showed that bronchiectasis was significantly associated with the occurrence of a recurrence (OR (95% CI): 2.6 (1.5–4.3)); p-value < 0.0001) (Table 4).

Table 4
Demographic and clinical variables predictive of recurrence in patients with hemoptysis

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age	< 40 years	Ref.	Ref.		
	40–54 years	1.3 (0.4–4.4)	0.63		
	55–70 years	1.6 (0.5–5.0)	0.41		
	> 70 years	1.9 (0.7–5.7)	0.23		
Sex male		0.9 (0.6–1.3)	0.51		
Severity of hemoptysis	Mild	Ref.	Ref.		
	Moderate	1.2 (0.8–2.0)	0.39		
	Severe	1.2 (0.8–2.0)	0.35		
Smoking history	≥ 10 pack/years	0.7 (0.4–1.1)	0.09		
	≥ 30 pack/years	0.9 (0.5–1.6)	0.74		
Antiplatelet therapy		0.9 (0.5–1.5)	0.69		
Anticoagulant therapy		1.1 (0.6–2.2)	0.75		
Antiplatelet + anticoagulant therapy		1.0 (0.6–1.6)	0.98		
Pneumonia/lung abscess		0.7 (0.4–1.3)	0.25		
Malignancy (primary and metastatic)		1.1 (0.6–1.9)	0.79		
Bronchiectasis		2.6 (1.5–4.3)	< 0.0001		
Acute bronchitis		0.6 (0.3–1.3)	0.18		
Cryptogenic hemoptysis		1.0 (0.5–2.1)	0.94		

Anticoagulant, antiaggregant, and anticoagulant plus antiaggregant drugs were not significantly associated with an increased risk of mortality and recurrence (Table 5).

Table 5

Role played by antiplatelet and anticoagulant therapy, alone and combined, on recurrence and mortality in patients with hemoptysis

Antiplatelet and anticoagulant therapy		No	Yes	p-value
Recurrence, n (%)		68 (20.1)	35 (18.8)	0.72
Recurrence severity, n (%)	Mild	49 (72.1)	25 (71.4)	0.46
	Moderate	17 (25.0)	7 (20.0)	
	Severe	2 (2.9)	3 (8.6)	
Median (IQR) n. recurrence events		1 (1–2)	1 (1–2)	0.12
Deaths after 18 months of follow-up, n (%)		50 (12.6)	33 (16.0)	0.24
Deaths for the disease which caused hemoptysis, n (%)		31 (62.0)	21 (63.6)	1.00
Antiplatelet therapy				
Recurrence, n (%)		80 (20.2)	23 (18.0)	0.58
Recurrence severity, n (%)	Mild	59 (73.8)	15 (65.2)	0.16
	Moderate	19 (23.8)	5 (21.7)	
	Severe	2 (2.5)	3 (13.0)	
Median (IQR) n. recurrence events		1.5 (1–2)	1 (1–2)	0.04
Deaths after 18 months of follow-up, n (%)		60 (13.0)	23 (16.0)	0.37
Deaths for the disease which caused hemoptysis, n (%)		35 (58.3)	17 (73.9)	0.19
Anticoagulant therapy				
Recurrence, n (%)		91 (19.7)	12 (19.7)	0.98
Recurrence severity, n (%)	Mild	64 (70.3)	10 (83.3)	0.85
	Moderate	22 (24.2)	2 (16.7)	
	Severe	5 (5.5)	0 (0.0)	
Median (IQR) n. recurrence events		1 (1–2)	2 (1–2)	0.66
Deaths after 18 months of follow-up, n (%)		71 (13.2)	12 (18.5)	0.24
Deaths for the disease which caused hemoptysis, n (%)		47 (66.2)	5 (41.7)	0.10

Discussion

To the best of our knowledge this is the largest prospective study describing the long-term prognostic outcomes (18 months) of patients with hemoptysis.

An overall mortality rate of 13.7% was found; the number of deaths increased from 18.1–31% after one year of follow-up and, then, decreased to 8.4% at the end of the study period. Most of the deaths occurring during the follow-up were related to the etiology which caused the hemoptysis, with pulmonary neoplasms being the leading cause.

Malignancy, which was reported as the most frequent etiology in patients with hemoptysis in several studies^{3–6,8,11}, represents the only significant predictor of mortality in our study.

Hemoptysis related to bronchiectasis, lower respiratory tract infections, and other less frequent etiologies showed a positive prognosis.

Two previous prospective studies based on poor sample size and on a follow-up of 1.8–2.7 years, described a slightly higher mortality rate (19.5–22%)^{7,8}, mainly driven by malignancies⁸.

More heterogeneous findings were reported by recently published European retrospective studies where lung cancer was the major cause of death, but the mortality rate ranged from 5.9 to 27%^{2,6,10}. Petersen et al. showed that increasing age, previous diagnosis of lung cancer, current/previous smoking history, and concomitant lung diseases are independent risk factors of death¹⁰. Notably, cryptogenic hemoptysis accounted for 80.5% of the diagnoses in this cohort, suggesting a suboptimal or difficult-to-perform diagnostic assessment¹⁰.

Recurrence rate was 17%, with bronchiectasis being the leading cause (27.2%), and the most important predictor of recurrence.

Bronchiectasis recurrences were mainly mild in contrast with those caused by lung malignancies (*i.e.*, the second most frequent cause of recurrence) which were equally mild and moderate.

Few recent retrospective data are available in the scientific literature. According to our findings, Fidan et al. and Ryuge et al., found bronchiectasis as the most frequent diagnosis in recurrent hemoptysis^{12,13}. Abdulmalak et al. described a recurrence rate of 16.6% and 16.1% during a 3-year follow-up in 2008 and 2009, respectively². Cryptogenic hemoptysis, lower respiratory tract infections, and lung cancer were the most common etiologies of recurrences, with cryptogenic hemoptysis representing 50% of all causes.

Choi et al., who described a recurrence rate of 19.1%, demonstrated that aspergillosis, active bleeding, and blood clot at the bronchoscopy during the first evaluation were significantly associated with the risk of recurrence; however, they analyzed only patients with mild hemoptysis¹⁴. Similar findings were described by Lee et al. who found that active bleeding during bronchoscopy, smoking history > 40 years, and hypertension were the main predictors of recurrence. Notably, the etiology was not evaluated¹⁵.

As suggested by Lee et al. recurrences should alert physicians about undetected pathological findings^{16,17}.

In seven patients of our cohort recurrence was associated with a new clinical and radiological assessment and to an etiological change. Three patients initially diagnosed with idiopathic bleedings and pneumonia were subsequently diagnosed with lung cancer, in contrast with the study of Tsoumakidou et al. where lung cancer was not diagnosed in any patients with an initial etiology other than lung cancer⁷. On the contrary, Abdulmalak et al. described a highest rate of lung cancer during the follow-up of patients with a respiratory infection (10.4%)².

In our study, four patients initially diagnosed with acute bronchitis and COPD exacerbation based on clinical and chest X-ray findings were then diagnosed with bronchiectasis.

The present scientific evidence suggests the importance of a clinical and radiological follow-up in patients with bleedings of unknown origin and related to an acute lower respiratory tract infection, as well as a more accurate radiological assessment (*i.e.*, chest CT) in patients with hemoptysis and risk factors for bronchiectasis¹⁹. Very few data can be retrieved on the impact of antiplatelet or anticoagulant therapies on long-term prognostic outcomes. In a large retrospective cohort study, Lee et al. failed to demonstrate a potential role of aspirin on recurrence¹⁵. Similar findings were showed by Ryuge et al. who studied the mechanism of hemoptysis relapse in patients who underwent BAE: they demonstrated that antiplatelet and anticoagulant therapy did not increase recanalization, *i.e.* the most frequent mechanism underlying re-hemoptysis¹³.

We prospectively proved that these drugs, individually or in combination, did not change the risk of death and of recurrences.

Some study limitations can be found. The observational nature cannot help discriminate the role played by some medical conditions for the background noise of confounders. However, for ethical reasons it is currently the best methodological approach. Differences in some standard operating procedures in the recruited centers could affect some results in terms of diagnostic accuracy. However, the recruited hospitals were reference national centers and, then, the operating variability should be not relevant. Subgroup analyses by etiology could have affected the statistical power of some findings; future studies focused on specific etiologies could confirm our novel results.

Conclusions

In conclusion, our study shows a low mortality rate in patients with hemoptysis followed-up for a long period. Pulmonary malignancy is the main etiology and the main predictor of death in these patients, whereas bronchiectasis is the most frequent diagnosis associated with recurrence. Antiplatelet and/or anticoagulant therapy do not change the risk of death or recurrence. Follow-up is recommended in patients initially diagnosed with lower airways infections and those with idiopathic bleedings, to detect new or misdiagnosed lung malignancies.

Abbreviations

ml: millilitres

IQR: interquartile ranges

COPD: chronic obstructive pulmonary disease

Declarations

Ethics approval and consent to participate:

resolution n. 665 (18/07/2013), Comitato Etico Ospedale San Paolo, Milan, Italy

Consent for publication:

not applicable

Availability of data and materials:

the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

the authors declare that they have no competing interests

Funding:

none

Authors' contributions:

Guarantor: MM is the guarantor of the content of the manuscript, including the data and analysis. Author contribution: MM: contributions to the conception and design of the work, acquisition, and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PC: contributions to the conception and design of the work, acquisition, and interpretation of data for the work; revising the manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LS: contributions to the analysis and interpretation of data for the work; revising the manuscript critically for important

intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GS: contributions to the conception or design of the work,

analysis and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved-

GC, MP, FT, PP, AF, AA, SC, SG, MB, ACC, SM, FA, SDP, SC: acquisition of data for the work; revising the manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements:

not applicable

References

1. Mondoni M, Sferrazza Papa GF, Sotgiu G, Carlucci P, Pellegrino GM, Centanni S. [Haemoptysis: a frequent diagnostic challenge](#). Eur Respir J. 2016;47(1):348-50
2. Abdulmalak C, Cottenet J, Beltramo G, et al. [Haemoptysis in adults: a 5-year study using the French nationwide hospital administrative database](#). Eur Respir J. 2015;46(2):503-11
3. Quigley N, Gagnon S, Fortin M. [Aetiology, diagnosis and treatment of moderate-to-severe haemoptysis in a North American academic centre](#). ERJ Open Res. 2020;6(4):00204-2020
4. Vanni S, Bianchi S, Bigiarini S, et al. Management of patients presenting with haemoptysis to a Tertiary Care Italian Emergency Department: the Florence Haemoptysis Score (FLHASc). Intern Emerg Med 2018;13(3):397-404
5. Mondoni M, Carlucci P, Job S, et al. [Observational, multicentre study on the epidemiology of haemoptysis](#). Eur Respir J. 2018; 51(1): 1701813
6. Soares Pires F, Teixeira N, Coelho F, Damas C. [Hemoptysis—etiology, evaluation and treatment in a university hospital](#). Rev Port Pneumol. 2011;17(1):7-14
7. Tsoumakidou M, Chrysosfakis G, Tsiligianni I, Maltezas G, Siafakas NM, Tzanakis N. [A prospective analysis of 184 hemoptysis cases: diagnostic impact of chest X-ray, computed tomography, bronchoscopy](#). 2006;73(6):808-14
8. Uzun O, Atasoy Y, Findik S, Atici AG, Erkan L. [A prospective evaluation of hemoptysis cases in a tertiary referral hospital](#). Clin Respir J. 2010;4(3):131-8
9. Arooj P, Bredin E, Henry MT, et al. [Bronchoscopy in the investigation of outpatients with hemoptysis at a lung cancer clinic](#). Respir Med. 2018; 139:1-5
10. Petersen CL, Weinreich UM. [Five-year follow-up of hemoptysis with no malignancy suspected on chest computed tomography: recurrence, lung cancer and mortality](#). Eur Clin Respir J. 2019; 6(1):1616519

11. Hirshberg B, Biran I, Glazer M, Kramer MR. [Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital](#). 1997;112(2):440-4
12. Fidan A, Ozdoğan S, Oruç O, Salepçi B, Ocal Z, Cağlayan B. [Hemoptysis: a retrospective analysis of 108 cases](#). Respir Med. 2002;96(9):677-80
13. Ryuge M, Hara M, Hiroe T, et al. Mechanisms of recurrent haemoptysis after super-selective bronchial artery coil embolisation: a single-centre retrospective observational study. Eur Radiol. 2018;29(2):70
14. Choi J, Baik JH, Kim CH, et al. [Long-term outcomes and prognostic factors in patients with mild hemoptysis](#). Am J Emerg Med. 2018;36(7):1160-1165
15. Lee MK, Kim SH, Yong SJ, et al. [Moderate hemoptysis: recurrent hemoptysis and mortality according to bronchial artery embolization](#). Clin Respir J. 2015;9(1):53-64
16. Lee YJ, Lee SM, Park JS, et al. [The clinical implications of bronchoscopy in hemoptysis patients with no explainable lesions in computed tomography](#). Respir Med. 2012;106(3):413-9
17. Mondoni M, Carlucci P, Cipolla G, et al. [Bronchoscopy to assess patients with hemoptysis: which is the optimal timing?](#) BMC Pulm Med 2019;19(1):36
18. Expert Panel on Thoracic Imaging, Olsen KM, Manouchehr-Pour S, Donnelly EF, et al. [ACR Appropriateness Criteria Hemoptysis](#). J Am Coll Radiol. 2020;17(5S):S148-S159.