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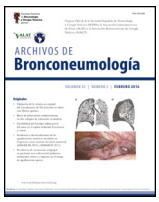

Scientific Letter

Predictors of Malignancy in Patients With Haemoptysis

Predictores de malignidad en pacientes con hemoptisis

Dear Editor,

Lung cancer often presents with haemoptysis[1–4] and is the only significant predictor of mortality in patients complaining of this symptom.[5] The diagnostic work-up of patients with haemoptysis should promptly rule out the presence of malignancy. Until now, no studies have specifically investigated the main predictors of malignancy in these patients. Despite a comprehensive diagnostic assessment at baseline (based on computed tomography (CT) and bronchoscopy), a subgroup of patients remains without an aetiological diagnosis (*i.e.*, idiopathic haemoptysis).[1–3,5–7] Previous studies described cases of lung cancer onset in patients initially diagnosed with idiopathic haemoptysis.[5,6,8] Thus, follow-up is needed in order to detect new or misdiagnosed lung neoplasms at an early stage.[5,6,8]

Some previous prospective studies have assessed the incidence of lung cancer and the overall survival of patients with idiopathic bleeding.[4,7–9]

The aim of the present study was to evaluate the main predictive factors for malignancy in patients with haemoptysis, based on initial and follow-up diagnostic work-up. Furthermore, the long-term prognosis and the incidence of lung cancer in patients with idiopathic haemoptysis were investigated.

This is a sub-analysis of an observational, prospective, multicentric, Italian study,[1] registered at ClinicalTrials.gov (identifier: NCT02045394). Written informed consent was signed by all participating patients[1] and subjects were followed-up for 18 months.[1,5]

From July 2013 to September 2015, consecutive adult (i.e., ≥18 years old) patients with haemoptysis were recruited.[1,5] Exclusion criteria were the following: (1) cause of haemoptysis already known; and (2) refusal to sign the informed consent.

The follow-up period lasted from December 2015 to February 2018.[5]

Severity of haemoptysis was graded based on the total amount of blood expectorated in 24 hours (h): 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).[1,5]

An ad hoc electronic database was created to collect all study variables. Qualitative data were described with absolute and relative (percentage) frequencies. Logistic regression analysis was performed to assess the relationship between demographic and clinical characteristics and malignancy diagnosis. The statistical software used for all the computations was Stata17.0 (StataCorp, College Station, TX, USA).

In total 451 out of 606 (74.7%) patients completed the follow-up,[1,3] 70/606 (11.5%) were lost, and 83/606 (13.7%) died during the follow-up. A total of 120 pulmonary malignancies were diagnosed (109 with primary lung cancers and 11 with pulmonary metastases).[1,5] At baseline, chest X-ray was performed in 119/120 (99.1%) patients, CT scan in 118/120 (98.3%) and bronchoscopy in 115/120 (95.8%).[1]

Univariate analysis showed that age ≥40 years (OR (95% CI): 10.3 (1.4–75.8); $P=0.02$), male sex (OR (95% CI): 1.99 (1.3–3.2); $P=0.003$), moderate and severe haemoptysis (respectively OR (95% CI): 1.8 (1.2–2.7); $P=0.006$ and OR (95% CI): 2.6 (0.8–7.9); $P=0.10$), smoking history ≥ 10 pack/years (OR (95% CI): 3.2 (1.9–5.5); $P<0.0001$), former airways neoplasm (OR (95% CI): 6.0 (3.1–11.9); $P<0.0001$) and abnormal findings at chest X-ray (i.e., consolidation and/or atelectasis and/or pleural effusion and/or mediastinal enlargement) (OR (95% CI): 6.4 (4.0–10.3); $P<0.0001$) were associated with the occurrence of a lung cancer. In the multivariate analysis only increasing age (OR (95% CI): 1.1 (1.0–1.2); $P=0.03$), former airways neoplasm (OR (95% CI): 22.1 (1.3–370.8); $P=0.03$), and abnormal chest X-ray (OR (95% CI): 32.0 (4.5–226.0); $P=0.001$) were significantly associated with an increased risk of malignancy (Table 1).

Overall, 54/606 (8.9%) patients were diagnosed with idiopathic haemoptysis (i.e. with negative CT and bronchoscopy). In 4/54 (7.4%) a lung cancer was diagnosed during the follow-up: in two patients after three months and in two after one year from the first evaluation. Three of these patients were smokers (smoking history > 30 pack/years). Three of the 54 (5.6%) patients with a final diagnosis of idiopathic bleeding died during the follow-up.

This is the largest prospective study on the predictors of malignancy in patients with haemoptysis.

Malignancy is one of the most common aetiologies for this symptom in Europe[1–4] and the leading cause of mortality in patients with haemoptysis.[5]

To date, no guidelines have recommended the best diagnostic approach in patients with haemoptysis, based on their clinical characteristics and malignancy risk factors.

In this study, we aimed to evaluate the main variables associated with malignancy, based on baseline and follow-up data. Patients showing such predictors deserve a prompt diagnostic assessment at baseline, with chest CT followed by bronchoscopy in cases of positive CT findings. Data on the utility of bronchoscopy in patients with haemoptysis and negative CT are still conflicting.[10–14]

Our study demonstrated that advancing age (from the age of 40), former airways neoplasms, and chest X-ray findings are the main predictors of malignancy. Mild (i.e. with a smoking history < 10 pack/years) or non-smokers with haemoptysis should be considered at risk of lung neoplasms when other risk factors are found, regardless of the amount of bleeding. Chest X-ray is usually the

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Table 1
Demographic and clinical variables predictive of malignancy.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age, years	1.0 (1.0–1.1)	<0.0001	1.1 (1.0–1.2)	0.03
Age				
≥40 years	10.3 (1.4–75.8)	0.02		
≥50 years	9.9 (3.1–31.8)	<0.0001		
Male sex	1.99 (1.3–3.2)	0.003	0.8 (0.1–4.5)	0.08
Severity of haemoptysis				
Mild	Ref.	Ref.		
Moderate	1.8 (1.2–2.7)	0.006		
Severe	2.6 (0.8–7.9)	0.10		
Smoking history				
≥10 pack/years	3.2 (1.9–5.5)	<0.0001	5.7 (0.8–40.3)	0.08
≥30 pack/years	6.0 (3.1–11.9)	<0.0001		
Former airways malignancy	6.0 (3.1–11.9)	<0.0001	22.1 (1.3–370.8)	0.03
Positive chest X-ray (one of: consolidation, atelectasis, mediastinal enlargement, pleural effusion)	6.4 (4.0–10.3)	<0.0001	32.0 (4.5–226.0)	0.001
Number of recurrences	0.4 (0.1–0.8)	0.02	1.0 (0.3–3.6)	0.99
Severity of haemoptysis recurrence				
Mild	Ref.	Ref.		
Moderate	4.8 (1.7–13.5)	0.003		
Severe	3.8 (0.6–25.5)	0.17		

first radiological investigation in the diagnostic work-up of patients with respiratory symptoms[1,2,7,15]; for this technique a sensitivity of 75.4% in symptomatic patients with lung cancer was found, with haemoptysis being the symptom most strongly associated with a diagnosis of lung neoplasm.[15]

Our data confirm the findings of Arooj et al. who failed to demonstrate a significant difference in lung cancer incidence between smokers and non-smokers in a cohort of 337 patients with haemoptysis, suggesting that smoking status should not influence the type of investigations undertaken in this patient category.[11–14]

Idiopathic haemoptysis showed an overall mortality of 5.5%. Lung cancer was diagnosed in four patients during the first year of follow-up; three of whom were smokers with a smoking history > 30 pack/years. Thus, the follow-up of patients with idiopathic bleeding is needed when lung cancer risk factors are present.

Few prospective studies have described long-term prognosis and lung cancer incidence of patients with idiopathic haemoptysis. Uzun et al. reported no deaths during a 1.8-year follow-up[4] whereas Savale et al. and Tsoumakidou et al. reported no new lung cancer cases.[7,9]

Retrospective studies showed heterogenous prognostic outcomes and differences in the definition of idiopathic haemoptysis.

Herth et al. described a 13% mortality during a 6.6 years follow-up and a 6% of lung cancer incidence within three years of follow-up. Only some patients underwent CT scan at the initial assessment.[8] Lee et al. found no lung cancers in 228 patients with negative CT scans during a follow-up of two years.[15]

Finally, Abdulmalak et al. described idiopathic haemoptysis in 50% of the cases at the initial assessment, with a 9.6% incidence of lung cancers within three years of follow-up.[6]

There are some limitations of our study. Firstly, the study lacks a control group. Furthermore, in the absence of international guidelines recommending the best diagnostic approach in patients with haemoptysis, a standardized diagnostic protocol was not implemented, and the clinical choices depended on centre experience and clinical assessment. However, our study described real-world settings, then, with a high external validity.

In conclusion, our study showed that advancing age, former airways neoplasms, and positive chest X-ray are the most important predictors of malignancy in patients with haemoptysis. This subgroup of patients deserves a prompt and comprehensive diagnostic evaluation at baseline (i.e., CT scan and bronchoscopy), regardless of the severity of the symptom and the smoking status. Follow-up is recommended in smokers with idiopathic bleeding: despite an overall good prognosis, lung cancer can still occur.

Authors' 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, GC, NV, AF, PP, AA, SG, AC, SM, RR, SP, FF, GV, SC: contributions to the 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 manuscript; final approval of the version and

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References

1. Mondoni M, Carlucci P, Job S, Parazzini EM, Cipolla G, Pagani M, et al. Observational, multicentre study on the epidemiology of haemoptysis. Eur Respir J. 2018;51:1701813.
2. 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;6:00204–2020.
3. Vanni S, Bianchi S, Bigiarini S, Casula C, Brogi M, Orsi 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;13:397–404.
4. 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;4:131–8.
5. Mondoni M, Carlucci P, Cipolla G, Pagani M, Tursi F, Fois A, et al. Long-term prognostic outcomes in patients with haemoptysis. Respir Res. 2021;22:219.
6. Abdulmalak C, Cottenet J, Beltramo G, Georges M, Camus P, Bonniaud P, et al. Haemoptysis in adults: a 5-year study using the French nationwide hospital administrative database. Eur Respir J. 2015;46:503–11.
7. Tsoumakidou M, Chrysofakis G, Tsiligianni I, Maltezakis G, Siafakas NM, Tzanakis N. A prospective analysis of 184 hemoptysis cases: diagnostic impact of chest X-ray, computed tomography, bronchoscopy. Respiration. 2006;73:808–14.
8. Herth F, Ernst A, Becker HD. Long-term outcome and lung cancer incidence in patients with hemoptysis of unknown origin. Chest. 2001;120:1592–4.
9. Savale L, Parrot A, Khalil A, Antoine M, Théodore J, Carette MF, et al. Cryptogenic hemoptysis: from a benign to a life-threatening pathologic vascular condition. Am J Respir Crit Care Med. 2007;175:1181–5.
10. Lee YJ, Lee SM, Park JS, Yim JJ, Yang SC, Kim YW, et al. The clinical implications of bronchoscopy in hemoptysis patients with no explainable lesions in computed tomography. Respir Med. 2012;106:413–9.
11. Arooj P, Bredin E, Henry MT, Khan KA, Plant BJ, Murphy DM, et al. Bronchoscopy in the investigation of outpatients with hemoptysis at a lung cancer clinic. Respir Med. 2018;139:1–5.
12. Bønløkke S, Guldbrandt LM, Rasmussen TR. Bronchoscopy in patients with haemoptysis and normal computed tomography of the chest is unlikely to result in significant findings. Dan Med J. 2015;62:A5123.
13. Mondoni M, Carlucci P, Cipolla G, Fois A, Gasparini S, Marani S, et al. Bronchoscopy in patients with hemoptysis and negative imaging tests. Chest. 2018;153:1510–1.
14. Kennedy MP, Arooj P, Henry MT. Bronchoscopy is not required in patients being investigated for hemoptysis at a rapid access cancer clinic with normal CT scan. Chest. 2018;154:465–6.
15. Bradley SH, Hatton NLF, Aslam R, Bhartia B, Callister ME, Kennedy MP, et al. Estimating lung cancer risk from chest X-ray and symptoms: a prospective cohort study. Br J Gen Pract. 2020, bjgp20X713993.

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