Observational, multicentre study on the epidemiology of haemoptysis

To the editor:

Haemoptysis, which is a challenging symptom accounting for 10–15% of all pulmonology consultations, may be associated with life-threatening medical conditions such as lung cancer [1–7].

Its aetiology and epidemiology vary widely among studies according to geographic locations and time of publication, epidemiological design, and diagnostic tests employed [2–8]. Bronchiectasis, malignancies, post-tuberculosis sequelae, and idiopathic bleedings have been recognised as the most frequent causes of haemoptysis in Europe over the last decade [3–7]. No guidelines exist suggesting an optimal work-up of symptoms, and data on the diagnostic yield of the most commonly prescribed examinations are limited [8].

The aim of this observational, prospective, multicentre study was to investigate the haemoptysis aetiology in association with its severity in an Italian population. We also evaluated the diagnostic yield of the prescribed diagnostic tests.

The study was approved by the ethical committees of five Italian participating hospitals and registered at ClinicalTrials.gov (identifier: NCT02045394). Written informed consent was signed by the recruited patients, who were followed-up for 18 months. Herein, we report the findings of the baseline assessment.

From July 2013 to September 2015, consecutive adult (*i.e.* ⩾18 years old) patients with haemoptysis were considered eligible. The following were considered as exclusion criteria: 1) aetiology of haemoptysis already detected (*e.g.* proven cancer-related and/or bronchiectasis-related haemoptysis); and 2) refusal to sign the informed consent.

Patients were divided into three groups on the basis of the total amount of blood expectorated in 24 h [2, 3, 9]: mild (*i.e.* drops of blood to 20 mL in 24 h), moderate (*i.e.* 20–500 mL in 24 h), and severe (*i.e.* >500 mL in 24 h).

All enrolled patients underwent physical examination and blood analysis. Subsequent tests deemed necessary for the diagnosis (*i.e.* sputum cultures, chest radiography, multi-detector chest computed tomography (CT), bronchoscopy, otorhinolaryngological evaluation, angiography) were chosen by the attending clinician on the basis of the clinical hypothesis and the symptom-driven diagnostic protocols of each hospital involved in the study.

Final diagnosis was established in each centre, on the basis of the clinical and imaging evidence, by a multidisciplinary consensus that involved pulmonologists, radiologists, pathologists and otorhinolaryngologists.

An electronic *ad hoc* form was created to collect demographic, epidemiological and clinical variables. Absolute and relative frequencies were used to summarise qualitative variables. Quantitative variables, for which the non-parametric distribution was assessed with the Shapiro–Wilk test, were summarised with medians and interquartile ranges (IQRs). 95% confidence intervals were computed to provide an interval estimation. The statistical software used for all the computations was Stata13.0 (StataCorp, College Station, TX, USA).

During the study period, 606 patients (median age 67 (IQR 52–76) years) were enrolled. More than half (327/606, 54.0%; 95% CI 50.0–57.9%) had a positive smoking history and most of them (404/606, 66.7%; 95% CI 62.8–70.3%) were male. The majority (424/606, 70.0%; 95% CI 66.2–73.5%) had mild

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TABLE 1 Haemoptysis aetiologies related to symptom severity and diagnostic tests prescribed for the assessment of aetiology and their diagnostic yield

Disease	Total	Mild	Moderate	Severe
Pulmonary malignancy	116 (19.1; 95% CI 16.2–22.5)	67/116 (57.8; 95% CI 48.7–66.4)	44/116 (37.9; 95% CI 29.6–47.0)	5/116 (4.3; 95% CI 1.9–9.7)
Lung cancer	106	63/106 (59.4; 95% CI 49.9–68.3)	39/106 (36.8; 95% CI 28.2–46.3)	4/106 (3.8; 95% CI 1.5–9.3)
Pulmonary metastasis	10	4/10 (40.0; 95% CI 16.8–68.7)	5/10 (50.0; 95% CI 23.7–76.3)	1/10 (10.0; 95% CI 1.8–40.4)
Pneumonia/lung abscess	113 (18.6; 95% CI 15.7–21.9)	94/113 (83.2; 95% CI 75.2–89.0)	19/113 (16.8; 95% CI 11.0–24.8)	0/113 (0.0; 95% CI 0.0–3.3)
Bronchiectasis	90 (14.9; 95% CI 12.2–17.9)	58/90 (64.4; 95% CI 54.2–73.6)	30/90 (33.3; 95% CI 24.5–43.6)	2/90 (2.2; 95% CI 0.6–7.7)
Acute bronchitis	83 (13.7; 95% CI 11.2–16.7)	69/83 (83.1; 95% CI 73.7–89.7)	14/83 (16.9; 95% CI 10.3–26.3)	0/83 (0.0; 95% CI 0.0–4.4)
Idiopathic haemoptysis	55 (9.1; 95% CI 7.0–11.6)	40/55 (72.7; 95% CI 59.8–82.7)	15/55 (27.3; 95% CI 17.3–40.2)	0/55 (0.0; 95% CI 0.0–6.5)
COPD (stable and exacerbated)	43 (7.1; 95% CI 5.3–9.4)	35/43 (81.4; 95% CI 67.4–90.3)	8/43 (18.6; 95% CI 9.7–32.6)	0/43 (0.0; 95% CI 0.0–8.2)
Active tuberculosis	20 (3.3; 95% CI 2.1–5.0)	12/20 (60.0; 95% CI 38.7–78.1)	6/20 (30.0; 95% CI 14.5–51.9)	2/20 (10.0; 95% CI 2.8–30.1)
Other pulmonary/bronchial vascular lesion	16 (2.6; 95% CI 1.6–4.2)	8/16 (50.0; 95% CI 28.0–72.0)	5/16 (31.3; 95% CI 14.2–55.6)	3/16 (18.8; 95% CI 6.6–43.0)
Interstitial lung disease	16 (2.6; 95% CI 1.6–4.2)	11/16 (68.8; 95% CI 44.4–85.8)	5/16 (31.3; 95% CI14.2–55.6)	0/16 (0.0; 95% CI 0.0–19.4)
Upper airways bleeding disease	11 (1.8; 95% CI 1.0–3.2)	6/11 (54.6; 95% CI 28.0–78.7)	5/11 (45.5; 95% CI 21.3–72.0)	0/11 (0.0; 95% CI 0.0–25.9)
Post-tuberculosis sequelae	10 (1.7; 95% CI 0.9–3.0)	3/10 (30.0; 95% CI 10.8–60.3)	6/10 (60.0; 95% CI 31.3–83.2)	1/10 (10.0; 95% CI 1.8–40.4)
Cardiopathy	8 (1.3; 95% CI 0.7–2.6)	5/8 (62.5; 95% CI 30.6–86.3)	3/8 (37.5; 95% CI 13.7–69.4)	0/8 (0.0; 95% CI 0.0–32.4)
Pulmonary embolism	5 (0.8; 95% CI 0.4–1.9)	4/5 (80.0; 95% CI 3.6–96.4)	1/5 (20.0; 95% CI 3.6–62.4)	0/5 (0.0; 95% CI 0.0–43.4)
Anticoagulant and antiplatelet therapy	4 (0.7; 95% CI 0.3–1.7)	1/4 (25.0; 95% CI 4.6–69.9)	3/4 (7.0; 95% CI 30.1–95.4)	0/4 (0.0; 95% CI 0.0–49.0)
Aspergilloma	3 (0.5; 95% CI 0.2–1.4)	1/3 (33.3; 95% CI 6.1–79.2)	2/3 (66.7; 95% CI 20.8–93.9)	0/3 (0.0; 95% CI 0.0–56.1)
Atypical mycobacteriosis	3 (0.5; 95% CI 0.2–1.4)	3/3 (100.0; 95% CI 43.9–100.0)	0/3 (0.0; 95% CI 0.0–56.1)	0/3 (0.0; 95% CI 0.0–56.1)
Tracheal granuloma (post-intubation/tracheostomy)	3 (0.5; 95% CI 0.2–1.4)	2/3 (66.7; 95% CI 20.8–93.9)	1/3 (33.3; 95% CI 6.1–79.2)	0/3 (0.0; 95% CI 0.0–56.1)
Coagulation disorder	3 (0.5; 95% CI 0.2–1.4)	2/3 (66.7; 95% CI 20.8–93.9)	1/3 (33.3; 95% CI 6.1–79.2)	0/3 (0.0; 95% CI 0.0–56.1)
Tracheobronchopathia osteochondroplastica	1 (0.2; 95% CI 0.0–0.9)	1/1 (100.0; 95% CI 20.7–100.0)	0/1 (0.0; 95% CI 0.0–79.3)	0/1 (0.0; 95% CI 0.0–79.3)
Bronchopleural fistula	1 (0.2; 95% CI 0.0–0.9)	1/1 (100.0; 95% CI 20.7–100.0)	0/1 (0.0; 95% CI 0.0–79.3)	0/1 (0.0; 95% CI 0.0–79.3)
Bronchiolitis	1 (0.2; 95% CI 0.0–0.9)	0/1 (0.0; 95% CI 0.0–79.3)	1/1 (100.0; 95% CI 20.7–100.0)	0/1 (0.0; 95% CI 0.0–79.3)
Asthma (exacerbated)	1 (0.2; 95% CI 0.0–0.9)	1/1 (100.0; 95% CI 20.7–100.0)	0/1 (0.0; 95% CI 0.0–79.3)	0/1 (0.0; 95% CI 0.0–79.3)

Diagnostic test	Performed/total	Pathological/performed
Sputum culture	167/606 (27.6; 95% CI 24.2–31.2)	24/167 (14.4; 95% CI 9.9–20.5)
Chest radiography	556/606 (91.7; 95% CI 89.3–93.7)	279/556 (50.2; 95% CI 46.0–54.3)
Otorhinolaryngologic examination	122/606 (20.1; 95% CI 17.1–23.5)	11/122 (9.0; 95% CI 5.1–15.4)
Angiography	13/606 (2.2; 95% CI 1.3–3.6)	13/13 (100.0; 95% CI 77.2–100.0)
CT scan	551/606 (90.9; 95% CI 88.4–93.0)	426/551 (77.3; 95% CI 73.6–80.6)
Bronchoscopy	487/606 (80.4; 95% CI 77.0–83.3)	237/487 (48.7; 95% CI 44.3–53.1)
CT scan and bronchoscopy	453/606 (74.7; 95% CI 71.2–78.2)	380/453 (83.9; 95% CI 80.2–87.0)

Data are presented as n or n (%). COPD: chronic obstructive pulmonary disease; CT: computed tomography.

haemoptysis; moderate and severe haemoptysis were recorded in 169/606 (27.9%; 95% CI 24.5–31.6%) and 13/606 (2.2%; 95% CI 1.3–3.6%) patients, respectively.

Pulmonary malignancy (116/606, 19.1%; 95% CI 16.2–22.5%), pneumonia/lung abscess (113/606, 18.6%; 95% CI 15.7–21.9%) and bronchiectasis (90/606, 14.9%; 95% CI 12.2–17.9%) were the most frequent causes of haemoptysis. Idiopathic haemoptysis was diagnosed in only 55/606 (9.1%; 95% CI 7.0–11.6%) patients (table 1).

The majority of neoplasms were lung cancers (106/116, 91.3%) with endobronchial lesions (84/116, 72.4%). Malignancies and bronchiectasis were the leading causes of moderate and severe haemoptysis, while pneumonia and acute bronchitis were the most frequent cause of mild bleeding (table 1).

The total number of prescribed diagnostic examinations and their diagnostic yield are shown in table 1. Chest radiography, CT scan and bronchoscopy, which were the most employed tests, had a diagnostic yield of 50.2% (95% CI 46.0–54.3%), 77.3% (95% CI 73.6–80.6%) and 48.7% (95% CI 44.3–53.1%), respectively. The combination of CT and bronchoscopy showed a diagnostic yield of 83.9% (95% CI 80.2–87.0%). The majority of bronchoscopies (472/487, 96.5%) were performed with the flexible instrument, while 13/487 (2.7%) were performed with the rigid scope.

This is, to our best knowledge, the largest prospective study specifically designed to evaluate the epidemiology of haemoptysis and its severity in a high-income country.

Our results show that pulmonary malignancy is the most frequent (19.1%) aetiology, with endobronchial lung cancer being the main type. However, pneumonia (18.6%), bronchiectasis (14.9%) and acute bronchitis (13.7%), mostly inducing mild bleeding, are frequent causes of haemoptysis.

Notably, a recent study performed in an Italian emergency department showed similar frequencies for three aetiologies (*i.e.* malignancy, pneumonia and bronchiectasis) [6]. Moreover, malignancy was the most important case of haemoptysis in a recent study carried out in Turkey [10].

Our results show some differences in comparison with other retrospective studies performed in Europe over the last decade. They showed that bronchiectasis, post-TB sequelae and idiopathic haemoptysis were the most important causes [3–5, 7]. Although malignancies were less frequent than other aetiologies, their percentage (13%–17.8%) was only slightly lower than that found in our cohort [3–5]. Bronchiectasis and respiratory infections such as pneumonia and acute bronchitis are frequent aetiologies in the latest European studies [3–7]. Bronchiectasis was also the main bleeding cause in recent epidemiological investigations performed in South Korea and Iran [11, 12].

Two European studies investigated the symptom aetiology based on hospital discharge diagnosis codes and found that cryptogenic haemoptysis was the most frequent cause (48.9–52.0%) [5, 7]. Idiopathic haemoptysis accounted only for 9% of all causes in our cohort, but its frequency might be slightly over-estimated as the present analysis does not include the follow-up assessment. In comparison with previous studies, we only considered those cases to be idiopathic in which all the examinations, including both radiological and endoscopic, failed to provide a diagnosis [2, 8, 13]. Furthermore, the use of the administrative coding system to estimate the epidemiology of a symptom might have biased their analysis, thus explaining the discrepancy with our data [5, 7].

For centuries, haemoptysis has been considered pathognomonic for pulmonary tuberculosis [2, 3]. In our cohort, active tuberculosis accounted only for 3.3% of all cases, confirming the low incidence recorded in Europe (0.3–10.0%) over the past decade [3–7]. In geographical areas with a higher TB incidence, TB remains a relevant cause of haemoptysis (15.0–24.8%) (*e.g.* in India it represents 79.2% of all causes) [11, 12, 14].

In terms of absolute frequency, neoplasms and bronchiectasis, which caused mild bleedings in the majority of the cases, were also the main causes of moderate-to-severe haemoptysis. Bronchiectasis is recognised as the leading cause of severe haemoptysis in recently reported studies [3, 11, 12, 15]. Notably, a Greek study, in which patients were classified following similar criteria adopted in our study, reported bronchiectasis as the first cause of moderate-to-severe haemorrhages [3].

It should be highlighted that no guidelines exist on an ideal staging method for the symptom severity. Therefore, we chose threshold values adopted in previous epidemiological studies [2, 3, 9].

Several diagnostic techniques are prescribed to assess the haemoptysis aetiology. Chest radiography, CT and bronchoscopy were the most frequently employed tools. While CT had the highest diagnostic yield, the combination of bronchoscopy and CT (diagnostic yield: 83.9%) was more effective and relevant than either test alone, confirming their synergistic role [2, 3, 11].

In conclusion, malignancy, bronchiectasis and pneumonia are the main haemoptysis aetiologies in our Italian cohort. Idiopathic bleeding shows a low incidence. Pneumonia and acute bronchitis are the leading

aetiologies of mild haemoptysis, while neoplasms and bronchiectasis are leading aetiologies of moderate-to-severe forms. Owing to their complementary role, the combination of bronchoscopy and CT has a high yield in the diagnostic work-up of patients with haemoptysis.

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