

Hemoptysis in Cancer Patients

Subjects: [Oncology](#) | [Emergency Medicine](#)

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Hemoptysis in cancer patients is a potentially serious symptom that requires detailed evaluation by oncologists and emergency department physicians. Timely diagnosis and appropriate management are crucial to address both the immediate concern of bleeding and the broader implications for the patient's cancer care. As hemoptysis in cancer patients indicates the presence of complications or progression of the disease, investigating the underlying cause using appropriate diagnostic procedures such as imaging studies (CT scans, bronchoscopy) and laboratory tests is vital, as it can significantly impact treatment choices and potentially alter the patient's overall prognosis. Risk stratification for cancer patients presenting with hemoptysis will support a personalized treatment approach that ensures that each patient receives tailored and effective care and identifies patients who are at a higher risk of deterioration, warranting more aggressive diagnostic and treatment plans and close, continuous monitoring for these patients.

hemoptysis

cancer

prediction score

lung cancer

etiology

Risk stratification

emergency department

1. Definition

Hemoptysis refers to the expectoration of blood, alone or mixed with mucus, from the lower respiratory system (i.e., below the vocal cords), and it engenders significant concern in the both the patient and healthcare team. Often, hemoptysis is minimal and related to an inflammatory or infectious etiology, and it typically entails less than 100 mL over 24 h ^{[1][2][3]}. Although massive hemoptysis is rare, it may account for 5% to 15% of episodes and should be treated as a life-threatening condition necessitating effective assessment and management ^[4]. Defining massive hemoptysis quantitatively has been a challenge and a source of debate in the literature. Prior definitions of massive hemoptysis range widely from greater than 200 mL to greater than 1000 mL of blood within 24 h ^{[3][5][6][7]}; further, the amount of blood reported by patients and their families is often under- or overestimated. Also, blood from the lower respiratory tract must be differentiated from that of the upper respiratory tract and/or the upper gastrointestinal tract. Moreover, clinical factors are often much more important in terms of outcomes and include the briskness of bleeding, the patient's ability to maintain a patent airway and expectorate blood, the availability of specialized support for therapeutic options, and the patient's underlying physiological reserve. With this in mind, major or massive hemoptysis can more practically be defined as hemoptysis that causes severe consequences resulting in aspiration of blood to the contralateral lung, airway obstruction, hypoxemia and respiratory failure

requiring additional respiratory support, including mechanical ventilation, severe anemia necessitating transfusion and, in extreme cases, even death [8][9].

2. Pathophysiology

The lung receives blood supply from two distinct sources: pulmonary arteries, which flow to the alveoli for gas exchange and are a low-pressure circulation, and bronchial arteries, which supply oxygenated blood to the bronchi and visceral pleura and are a high-pressure circulation [10][11]. Although the bronchial arteries make a smaller contribution to pulmonary blood flow than the pulmonary arteries, they more frequently give rise to hemoptysis, especially when they undergo neovascularization in the presence of inflammatory diseases. These newly developed bronchial arteries are ensconced within smooth muscle fibers that can contract in response to diverse stimuli, increasing the risk of bleeding. Effective elimination of this neovascular vessel network can be achieved through arterial embolization. On the other hand, vasospasms in the pulmonary arterial network are comparatively weak, as these vessels possess thin and delicate walls that lack active contractile properties [10][11]. Pulmonary arterial hemorrhage typically arises from ulceration of the vessel wall, which may be due to lung cancer or other diseases. In such cases, bleeding is often transiently controlled by clot formation. However, the risk of rebleeding remains if the clot dissolves or the vessel wall ruptures again [10][11]. Unfortunately, it is not always possible to determine the arterial origin of the hemorrhage.

In the context of cancer, hemoptysis may occur through various pathophysiological mechanisms, impacting the amount and speed of the bleeding [12][13]. These include the formation of angiogenesis in and around the tumor, shedding of the tumor's outer layer, necrosis within the tumor, irritation caused by coughing, erosion of airway tissue into nearby blood vessels and bleeding resulting from medical procedures or treatments [12][13]. Certain therapies targeting vascular endothelial growth factor (VEGF), such as bevacizumab, may also result in hemoptysis due to the distribution of endothelial cell regulation reversing the protective effect of VEGF on endothelial cells [14][15], as well as fistulous tracts when such agents are combined with radiation [16][17]. Other medications, including anticoagulants and antiplatelet therapies that are commonly used in cancer patients, can also cause or exacerbate bleeding.

3. Etiology

Hemoptysis can arise from a diverse range of etiologies, including lung cavitation, infections, neoplastic conditions, pulmonary thromboembolic disease, cardiac dysfunction, including pulmonary edema or valvular abnormalities, hematological disorders, iatrogenic factors, sequelae from drugs or other substances, vascular anomalies, congenital lung malformations and idiopathic origins [18][19][20][21][22][23]. Examples of patients presented with hemoptysis in the setting of cancer are shown in **Figure 1** and **Figure 2**.

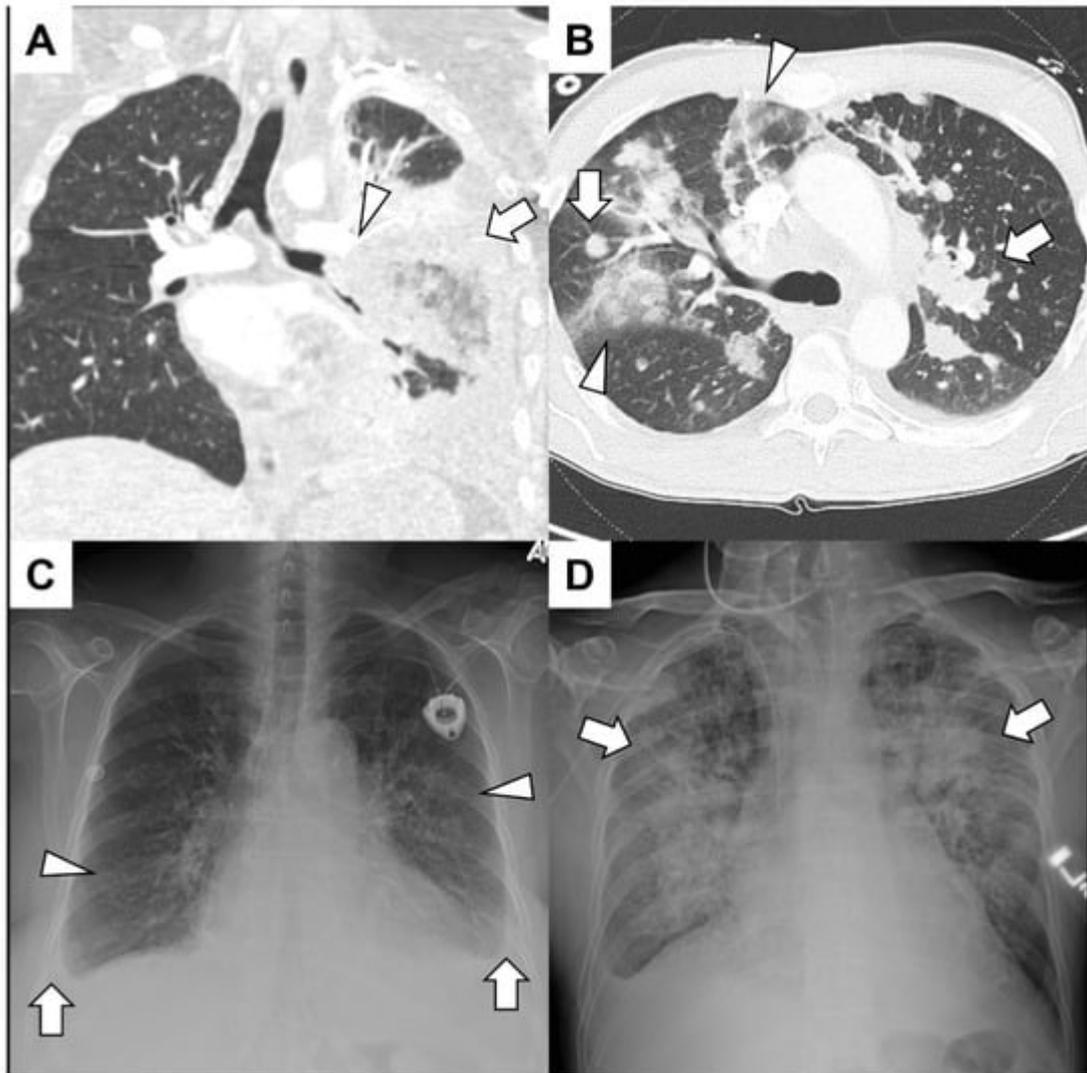


Figure 1. (A) A young man with acute lymphoid leukemia presented with significant hemoptysis. He had both neutropenia and lymphopenia due to recent treatments. A CT angiogram showed irregular soft-tissue encasement of the lower-order branches of the left pulmonary artery (arrowhead) and consolidation (arrow) and air bronchograms in the left lower lobe. Bronchoscopy revealed that the left lower lobe collapsed without endobronchial lesions. Surgical intervention with left lower lobectomy confirmed invasive mucormycosis and left pulmonary artery branches were full of thrombi. (B) A middle-aged man with adenoid cystic cancer presented with hemoptysis mixed with mucus over the previous few weeks. A CT angiogram excluded pulmonary emboli but showed diffuse nodules and mass-like consolidation (arrows) along with ground glass infiltrates peripherally (arrowhead). No endobronchial component was identified, and since the hemoptysis was of a small volume, no further intervention was warranted. (C) An elderly woman with a history of Hodgkin lymphoma presented with hemoptysis, dyspnea and a syncopal episode. A chest radiograph demonstrated bilateral infiltrates (arrowheads) and small bilateral effusion (arrows) with blunting of the costophrenic angles. She had volume overload with pulmonary edema, and an echocardiogram demonstrated severe aortic valve stenosis. (D) A patient with acute myelogenous leukemia after hematopoietic allogeneic stem cell transplantation from a matched sibling presented with hemoptysis and epistaxis. A chest radiograph showed bilateral diffuse infiltrates (arrows), and a bronchoscopy

revealed blood-tinged secretions throughout the tracheobronchial tree. He had diffuse alveolar hemorrhage due to thrombotic microangiopathy related to calcineurin inhibitors.

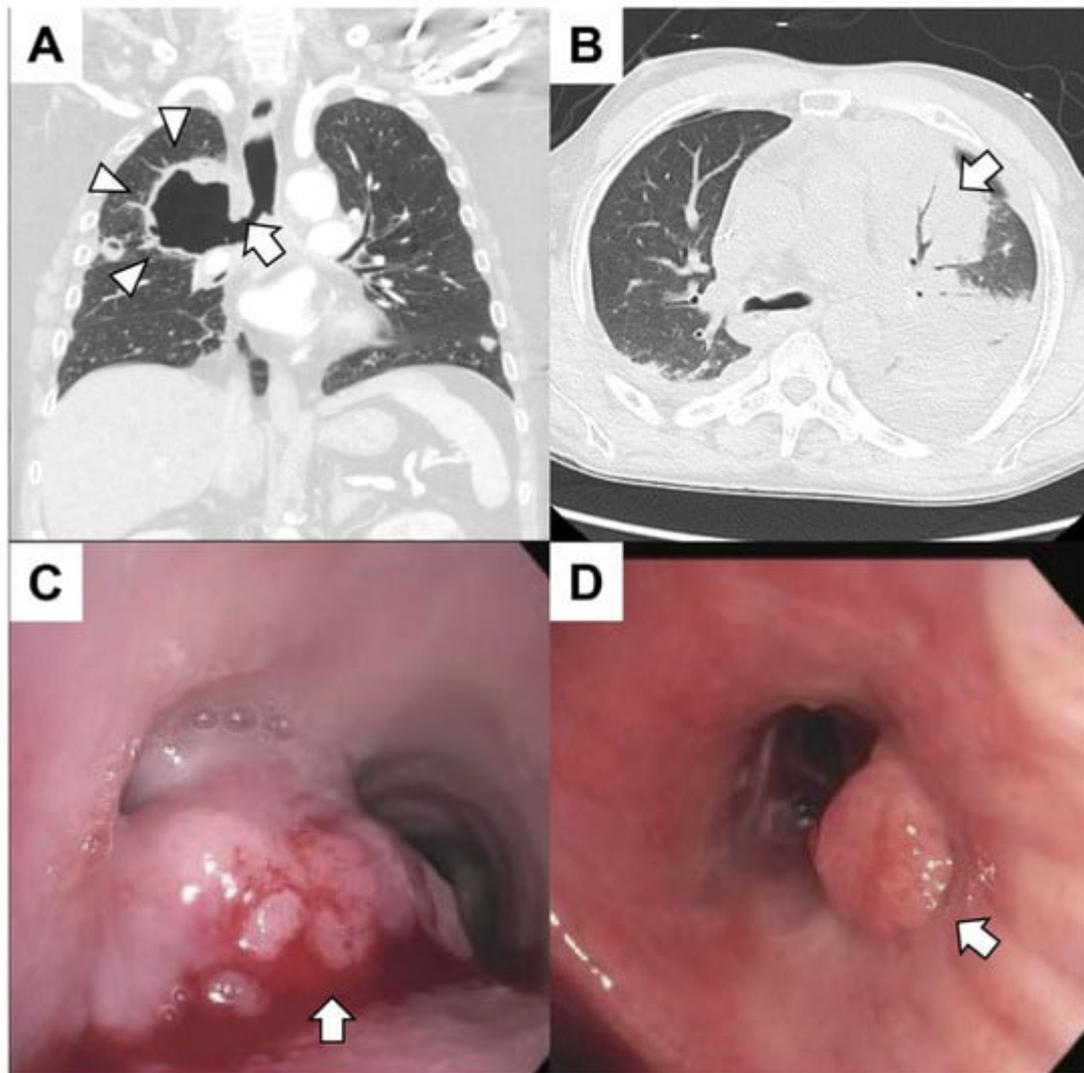


Figure 2. (A) A patient with metastatic lung cancer treated with radiation 1 month prior to the right upper lobe presented with hemoptysis. The coronal CT of the chest revealed a cavitary lesion (arrowheads) contiguous with the right mainstem bronchus (arrow). The patient expired from massive hemoptysis shortly after presenting to the emergency center. (B) A patient with leukemia with pancytopenia (white blood cells $0.0 \times 10^9/L$ platelets $14,000 \times 10^9/L$) and fever presented with hemoptysis. The patient had sepsis with bacteremia. A chest CT revealed consolidation in the left upper lobe (arrow) with air bronchograms. (C) A patient with gastroesophageal junction cancer presented with dyspnea and mild hemoptysis. Bronchoscopy revealed a mass at the main carina obstructing 90% of the left mainstem and 20% of the right mainstem. The mass (arrow) was large, exophytic and friable. The tumor was debulked using rigid bronchoscopy, and argon plasma coagulation was used to achieve hemostasis. Biopsies were consistent with metastatic disease. (D) A patient with metastatic colorectal cancer had dyspnea and mild hemoptysis. The patient had mucopurulent and blood-tinged secretions emanating from the right middle lobe. An endoluminal tumor mass (arrow) obstructing the superior segment of the left lower lobe was found. The hemoptysis resolved after treatment of a respiratory infection.

Immune checkpoint inhibitor therapy is currently the standard of care for many types of malignancies and has dramatically changed the landscape for treating patients with cancer. Among the various immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy, diffuse alveolar hemorrhage (DAH) is a rare but a concerning and life-threatening side effect [24][25][26][27]. Also, certain antineoplastic therapies, severe thrombocytopenia, and post-hematopoietic allogeneic stem cell transplantation can cause hemoptysis in cancer patients. Characterized by dyspnea, cough and hemoptysis, DAH often necessitates bronchoscopic evaluation to guide diagnosis and differentiate cases with infectious, bland hemorrhage and connective tissue disease-associated causes from those induced by cytotoxic drugs and graft-versus-host disease [28]. The prognosis of DAH is poor, with in-hospital mortality ranging from 20% to 100%. Identifying the underlying etiology of hemoptysis is paramount to ensure timely and targeted therapeutic interventions and provide the necessary psychosocial support [18][19][20][21]. **Table 1** summarizes the common etiologies of hemoptysis and the causes of life-threatening hemoptysis [21][29][30][31].

Table 1. Etiology of hemoptysis in general and specific to cancer patients [21][29][30][31].

Category	Disease
Pulmonary	Neoplasm *, e.g., bronchogenic carcinoma (second most common cause)
	Broncho-vascular fistula resulting from bronchopleural fistula [32], causing massive hemoptysis
	Tumors infiltrating the bronchial wall [33]
	Transformation of adenocarcinoma into squamous cell carcinoma [34]
	Endobronchial tumors (may present with hemoptysis in 15% of patients)
	Infection
	Tuberculosis (most common cause worldwide)
	Acute viral or bacterial infection
	Mucormycosis [35]
	Staphylococcus aureus [36]
	Invasive aspergillosis [35]
	Aspergillus mycetoma (fungus ball)
	Strongyloidiasis [37]
	Nontuberculous mycobacterial (Ntm) [38]
Coccidioidomycosis [39]	
Actinomycosis [40]	
Pyogenic lung abscess [41]	
Cystic fibrosis	
Bronchiectasis *	
Lupus pneumonitis due to systemic lupus erythematosus	
Cardiac	Mitral stenosis *
	Congestive heart failure *
	Pulmonary hypertension
	Congenital heart disease *
Vascular	Pulmonary embolism
	Vasculitis
	Goodpasture syndrome
	Behcet disease

Category	Disease
	Granulomatosis with polyangiitis Pulmonary vascular fistula Vascular malformation (e.g., pulmonary artery aneurysm, arteriovenous malformations) * Pulmonary artery rupture Tracheoinnominate artery fistula Hereditary hemorrhagic telangiectasia
DAH * [42][43][44][45]	Typically presents with dyspnea, cough, hemoptysis and new alveolar infiltrates on chest imaging Hemoptysis is common but may be absent in up to one-third of patients
Hematologic	Anticoagulant use Coagulopathy Thrombocytopenia
Trauma	Airway trauma Lung contusion Foreign body
Iatrogenic	Injury to structures * during: Pulmonary artery catheterization Lung biopsy Airway stenting Right heart catheterization
Drugs and toxins	Penicillamine [46][47] Crack cocaine [22][48] Bevacizumab [13]
Other	Thoracic endometriosis (catamenial hemoptysis) Cryptogenic: no identified cause on CT or bronchoscopy (50% of cases in high-income countries) Idiopathic pulmonary hemosiderosis

4. Epidemiology of Hemoptysis

The epidemiology of hemoptysis varies widely based on geographic location, epidemiological study design and definitions of hemoptysis. Minor hemoptysis commonly results in outpatient clinic visits and hospital admissions, and hemoptysis comprises 10% to 15% of all pulmonary consultations [49]. Interestingly, in a recent observational, prospective multicenter study in Italy, malignancy, bronchiectasis and pneumonia were the main etiologies of hemoptysis; pneumonia and acute bronchitis resulted in mild hemoptysis, and neoplasms and bronchiectasis resulted in moderate to severe hemoptysis [49]. Massive hemoptysis is relatively infrequent, and the leading causes of massive hemoptysis worldwide include tuberculosis, bronchiectasis, mycetoma and cancer [8][49]. In the United States, hemoptysis is the reason for approximately 6.8% of visits to pulmonary clinics and is responsible for about 11% of admissions to pulmonary hospital services [8].

Approximately 20% of hemoptysis cases are caused by lung cancer, with 3% of lung cancer cases resulting in massive hemoptysis [12]. The highest incidence of bleeding is linked to squamous cell histology, and massive hemoptysis is linked to cavitation and tumors originating from or penetrating through the central airways [50][51]. According to Corey and associates, individuals with lung cancer and hemoptysis exhibited a mortality rate of 59%.

However, this figure escalated to 80% for those who experienced bleeding exceeding 1000 mL within a 24 h period in conjunction with a cancer diagnosis [52]. In addition, inpatient hospitalization, advanced age and a requirement for mechanical ventilation are independent predictors of in-hospital mortality among patients with nonsmall cell lung cancer [53]. Other mortality predictors include contralateral lung aspiration on radiography and hemodynamic instability [29]. Other tumors including thyroid, breast, colon and renal cancer, as well as melanoma, may also infiltrate the tracheobronchial tree, resulting in malignant airway obstruction and hemoptysis [54].

5. Presentations and Investigations for Hemoptysis in Cancer Patients

5.1. Primary Lung Cancer

In addition to hemoptysis, symptoms of lung cancer may include a new cough, shortness of breath, chest pain, unintended weight loss or recurrent respiratory infections. Pulmonary examination may demonstrate focal wheezing due to localized obstruction, reduced breath sounds with pleural effusion or lung mass, diffuse wheezing or a shift of the trachea in those with central airway obstruction [18][55]. More advanced findings include clubbing, cachexia or muscle weakness from a paraneoplastic syndrome.

Investigation of hemoptysis in those with suspicion of lung cancer typically starts with a chest radiograph. A chest radiograph could appear normal or reveal segmental atelectasis, lobar collapse, obstructive pneumonitis or pleural effusion. In those with an abnormal chest radiograph or significant risk factors (e.g., smokers, persistent hemoptysis, older), computed tomography (CT) of the chest with contrast and referral to a specialist is recommended [56]. A chest CT may show a range of abnormalities, from a solitary lung nodule to endobronchial obstruction with an atelectatic lobe or lung and/or pleural effusion, and contrast helps identify enlarged mediastinal/hilar lymphadenopathy and other vascular anomalies [18][55]. Bronchoscopy can help identify the source of bleeding, and, in cases with tumors, vascular lesions may obstruct airways distal to the tumor, and the mucosa may be friable or erythematous (**Figure 1C,D**). The tumor itself may be polypoid or papillary infiltrative with superficial erosions. When airway tumors outgrow their vascular supply, they tend to necrose, and deeper biopsies may be necessary in these cases [18][55].

Additionally, fluorodeoxyglucose (FDG)–positron emission tomography can reveal positive uptake of FDG in metabolically active nodules and lymph nodes, indicating the presence of active disease. However, such uptake can arise from various conditions, including malignancy, active infection or inflammatory lung diseases. False-positive results can occur in infectious or inflammatory granulomas, while false negatives may occur in sub-solid nodules and carcinoid tumors [18][55]. Uptake within the mediastinal lymph nodes helps to guide the subsequent staging and diagnosis with endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer [57].

5.2. Pulmonary Metastasis

Many cancers can metastasize to the lung, including melanoma, sarcomas and adenocarcinoma of the colon, breast, kidney or testicle [18][55]. Endobronchial lesions, in particular, can occur as metastases from renal cell carcinoma, thyroid carcinoma, esophageal cancer, ovarian cancer, melanoma, breast cancer, colorectal cancer and sarcomas. In addition to hemoptysis, symptoms from metastatic disease may include pain, weight loss, malaise, cough and dyspnea. A chest CT can reveal one or multiple nodules of various sizes, ranging from diffuse micronodular shadows (known as miliary) to well-defined masses, often irregular and located at the periphery of the lower lung zones. Some of these masses may also show signs of cavitation, and lymphadenopathy may be present [18][55]. Subsequent imaging to determine the primary site of the cancer may be required. Tissue diagnosis may be directed at other sites of disease or can be confirmed via bronchoscopic interventions.

6. Risk stratification of hemoptysis in patients with cancer

There are limited data on the risk stratification of hemoptysis in cancer patients. A retrospective study by Grosu et al. that focused on solid organ malignancies found that advanced-stage diseases, active bleeding and endobronchial lesions during initial bronchoscopic evaluation were independently associated with decreased survival [58]. On the other hand, higher hemoglobin levels at the time of bronchoscopy and bleeding control at 48 h were linked to improved survival [58]. In hospitalized patients, mortality risk was increased with mechanical ventilation at referral, cancer diagnosis, aspergillosis, chronic alcoholism, pulmonary artery involvement and extensive lung infiltrates upon admission [3][18]. These predictors offer valuable insight into the prognosis of cancer patients with hemoptysis.

Mondoni et al. examined the long-term prognostic outcomes of patients with hemoptysis after 18 months of follow-up [59]. The overall mortality rate was 13.7%, with 43.4% of deaths happening in the first 3 months after presentation. Most deaths during the follow-up period were directly attributed to the underlying causes of hemoptysis, which were primarily pulmonary neoplasms. Indeed, malignancy emerged as the most frequent cause of hemoptysis in various studies, with notably higher mortality rates observed in some prior prospective studies of hemoptysis compared to Mondoni et al.'s findings [59]. Recent retrospective European studies have shown more diverse mortality rates from hemoptysis, with lung cancer remaining the primary cause of death [60][61][62]. Several independent risk factors for mortality in hemoptysis patients were advanced age, previous lung cancer diagnosis, smoking history and concurrent lung diseases [60].

In a study by Fartoukh et al., the severity of hemoptysis was assessed, and a scoring system was developed to predict in-hospital mortality. The overall in-hospital mortality rate was 6.5%, and independent predictors of mortality included chronic alcoholism, cancer as an underlying cause of the hemoptysis, involvement of the pulmonary artery as the source of bleeding, the involvement of two quadrants or more on chest X-ray at the time of referral and the initial use of mechanical ventilation [3]. The researchers created a prediction score based on these factors, which accurately estimated the probability of death in hemoptysis patients [3] and demonstrated comparable discriminative capabilities to those of the Simplified Acute Physiology Score II (SAPS II), a commonly used tool to assess acute disease severity. Categorizing patients into mortality risk groups based on the prediction score can

enable physicians to plan appropriate treatment strategies, such as step-down facility management, vascular interventional radiology or ICU interventions [3].

Overall, the current literature sheds light on the long-term prognostic outcomes of patients with hemoptysis, emphasizing the significance of identifying the underlying cause, particularly malignancies, for predicting mortality. Additionally, these findings highlight the importance of developing a prediction score specific for cancer patients to assess the prognosis of patients with hemoptysis. The findings regarding mortality risk factors and prognosis in each study are summarized in **Table 2**.

Table 2. Summary of the risk factors and prognosis in the published literature.

Study/Author(s)	Cohort	Risk Factors for Mortality, Prognosis, Other Findings
Grosu et al. [58]	Retrospective Patients with solid organ tumors and mild hemoptysis N = 112	Upon multivariate analysis, factors independently associated with improved survival had higher hemoglobin values (HR 0.78; 95% CI, 0.67–0.91) and cessation of hemoptysis without recurrence at 48 h (HR 0.43; 95% CI 0.22–0.84). Variables independently associated with worse survival were disease stage (HR 10.8; 95% CI, 2.53–46.08) and active bleeding with endobronchial lesion (HR 3.20; 95% CI 1.74–5.89).
Fartoukh et al. [3]	Retrospective Consecutive patients admitted to ICU with hemoptysis N = 1087	Independent predictors of mortality were mechanical ventilation at the time of referral, cancer diagnosis, aspergillosis, chronic alcoholism, pulmonary artery involvement and infiltrates involving two or more quadrants upon admission. A model-based score for prognosis was developed that assigned 1 point for chronic alcoholism, pulmonary artery involvement and radiographic patterns and 2 points for cancer, aspergillosis and mechanical ventilation.
Hirshberg et al., Vanni et al., Soares et al., and Uzun et al. [6][62][63][64]	Analytical cohort studies	Malignancy was a leading cause of hemoptysis, with a decrease in mortality related to bronchiectasis, lower respiratory tract infections and other less frequent causes.
Uzun et al. and Tsoumakidou et al. [64][65]	Analytical cohort studies	Malignancy was a leading underlying cause of hemoptysis with mortality rates ranging from 19.5% to 22%.
Soares et al., Petersen et al., and Abdulmalak et al. [60][61][62]	Analytical cohort studies	Lung cancer was the primary cause. Reported mortality rates varied significantly, ranging from 5.9% to 27%.

Study/Author(s)	Cohort	Risk Factors for Mortality, Prognosis, Other Findings
Petersen et al. [60]	Retrospective Consecutive patients with no malignancy suspected on chest CT N = 609	Predictors of mortality were advanced age, a previous lung cancer diagnosis, a current or previous smoking history, and concurrent lung diseases.
Mondoni et al. [59][66]	2019 study: secondary analysis of an observational multicenter study N = 486 2021 study: prospective multicenter study N = 606	Recurrences indicated previously undetected pathological findings, as there was a recurrence of hemoptysis in 7 patients, of whom 3 were found to have lung cancer upon further investigation. Pulmonary neoplasms were the primary cause of death, and the overall mortality rate was 13.7%.
Tsoumakidou et al. [65]	Prospective cohort N = 184	No patients initially diagnosed with an etiology other than lung cancer were found to have lung cancer upon further investigation.
Abdulmalak et al. [61]	A 5-year retrospective cohort study N = 81,572	An initial diagnosis of respiratory infection with highest lung cancer detection rate (10.4%) during the follow-up, and lung cancer was the cause in 17.4% of patients.
Majhail et al. [67]	Prospective data review of patients who had hematopoietic stem cell transplantation (HSCT) with alveolar hemorrhage N = 116	Advanced age, utilization of an allogeneic donor source, administration of a myeloablative conditioning regimen and the occurrence of acute severe graft-versus-host-disease were identified as independent predictors associated with a heightened risk of alveolar hemorrhage following HSCT. The probability of 60-day survival from the onset of hemorrhage was determined to be 16% in the diffuse alveolar hemorrhage group and 32% for the idiopathic alveolar hemorrhage group. With the exception of 20 patients, all individuals in this study received a standard regimen of high-dose corticosteroids; among the patients who received corticosteroids, the 60-day survival rate was found to be 26%, while those who did not receive corticosteroids exhibited a 60-day survival rate of 25%.

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