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RESEARCH ARTICLE

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Clinical characteristics and anticoagulation patterns of patients with acute pulmonary thromboembolism and hemoptysis

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Abstract

Hemoptysis is a frequently encountered manifestation in cases of acute pulmonary thromboembolism (PTE), significantly impacting clinical decision-making. Despite its clinical relevance, studies focusing on patients with acute PTE and hemoptysis are notably scarce. In this retrospective study, we examined data from hospitalized patients with acute PTE at Peking Union Medical College Hospital (PUMCH) between January 2012 and October 2020. Among the 896 patients analyzed, 105 (11.7%) presented with hemoptysis. Patients with hemoptysis were younger, had higher RRs, and frequently reported chest pain, predominantly showing a negative sPESI score. A significant association with autoimmune diseases was observed (39.0% vs. 16.1%; $p < 0.001$), along with higher occurrences of pulmonary infections (29.5%), lung cancer (21.0%), and chronic heart failure (16.2%). Hemoptysis in PTE is multifactorial; 51.4% of cases were PTE-related, with 85.2% experiencing mild hemoptysis. Among patients with disease-related hemoptysis (13.3%), 90.9% with massive hemoptysis had underlying diseases, predominantly lung cancer. In 35.2% of cases, the cause of hemoptysis remained undetermined, with vasculitis accounting for 29.7%. Anticoagulation strategies varied with the severity of hemoptysis; 82.9% with mild and only 27.3% with massive hemoptysis received therapeutic-dose anticoagulation. Multivariate analysis identified massive hemoptysis as the most significant determinant of anticoagulation decisions. Patients with massive hemoptysis had the poorest outcomes, with an in-hospital mortality rate of 36.4% and 72.7% receiving reduced or no anticoagulation.

KEYWORDS
anticoagulants, prognosis, pulmonary embolism, treatment

INTRODUCTION

Pulmonary thromboembolism (PTE) is globally ranked as the third leading cause of cardiovascular mortality.[1] The clinical presentation of acute PTE varies, with the incidence of hemoptysis ranging from 2.6%–7.6%.[2–4] Although less prevalent compared to dyspnea and chest pain, the presence of hemoptysis serves as a crucial diagnostic indicator in acute PTE.[5] Hemoptysis in those patients may originate from the PTE itself, such as embolism-associated pulmonary infarction, or it may indicate underlying diseases. In cases where concurrent infectious diseases such as tuberculosis or aspergillosis coexist with PTE, hemoptysis often presents as massive, whereas lung cancer patients exhibit significant variability in the volume of hemoptysis.[6–8] When systemic vasculitis is associated with PTE, the presence of vasculitic involvement in the lungs, such as diffuse alveolar hemorrhage (DAH) or the formation of an arterial aneurysm, typically results in a substantial amount of hemoptysis.[9,10] In clinical practice, differentiating the underlying causes of hemoptysis solely based on the volume of blood expectorated is challenging due to the varying presentations. While mild to moderate bleeding is commonly observed in hemoptysis caused by PTE,[8,11] recent reports have also documented cases of massive hemoptysis.[12] Therefore, a comprehensive analysis and disease profiling are necessary for patients presenting with both PTE and hemoptysis.

The confluence of acute PTE and hemoptysis presents a challenge in determining the appropriate dosage of anticoagulant treatment strategies. Clinicians face the dilemma of potential exacerbation of hemoptysis with therapeutic-dose anticoagulation, while reducing anticoagulation to an intermediate dose may increase the risk of thrombosis progression. Although several case reports have extensively described this clinical challenge,[13–15] the real-world prevalence of different patient-selected anticoagulation strategies remains unknown, and current guidelines lack a comprehensive discussion on diagnostic and treatment pathways.[16–18]

Therefore, the purpose of our study is to bridge this knowledge gap by investigating the clinical characteristics, disease profiles, anticoagulation patterns, and outcomes of PTE patients who present with hemoptysis. We aim to comprehensively depict the clinical features in real-world scenarios for patients experiencing both embolism and hemoptysis. Through this exploration, we seek to establish a rational assessment process encountering such patients in clinical practice. Our study aims to provide additional clinical data and enhance our understanding of the optimal evaluation and management of patients in this situation.

MATERIALS AND METHODS

Study design

This is a single-center, retrospective, observational study. Consecutive inpatients aged 18 years or older, diagnosed with acute PTE in Peking Union Medical College Hospital (PUMCH) from January 1, 2012, to October 22, 2020, were enrolled on the hospital's electronic medical record system. The criteria of diagnostic and risk stratification followed the strategy given by the European Society of Cardiology (ESC) in the study. The diagnosis of PTE required to be confirmed with computed tomographic pulmonary angiography (CTPA), enhanced computed tomography of the chest, and scintigraphic ventilation-perfusion (V/Q) scan revealing a high probability of PTE. Transthoracic echocardiography was used in patients to assess right ventricular (RV) function. Chronic PTE and non-thromboembolism such as bone-cement embolism and lipiodol embolism were excluded. Patients with insufficient baseline clinical data for analysis were also excluded. This study was approved by the Institutional Review Board of the PPUMCH (Ethical review number: B164) according to the Declaration of Helsinki. Informed consent was signed by the participants or their authorized family members.

Data collection

Patients enrolled in this study had data recorded that included demographic information, symptoms and signs, comorbidities, admission laboratory tests, imaging examinations and therapeutic management in the hospital. Pulmonary embolism severity index (PESI)[16] and simplified pulmonary embolism severity index (sPESI)[16] were calculated for all patients. Cardiac biomarkers used in the risk assessment of PTE include cardiac troponin I (cTnI) and N terminal pro-B-type natriuretic peptide (NT-proBNP). Patients with cardiac arrest, obstructive shock, or persistent hypotension were defined as high-risk PTE. Patients who had positive sPESI scores together with either RV dysfunction (by echocardiography or CTPA) or elevated cardiac biomarker levels in the circulation (elevated cTnI or natriuretic peptide concentrations in plasma) were classified as intermediate-risk patients. PTE patients with negative sPESI score were classified as low-risk. Standard therapeutic-dose anticoagulation dose anticoagulation: This complies with the therapeutic dosing recommendations of the 2019 ESC. For example, low molecular weight heparin (LMWH) dosages are adjusted based on body weight or administered at full therapeutic doses (e.g., dalteparin 100 U/kg

every 12 h, or enoxaparin 1 mg/kg every 12 h); for heparin anticoagulation, the target APTT is 1.5–2.5 times the baseline value; for direct oral anticoagulants, taking rivaroxaban as an example, patients with normal renal function receive 15 mg twice daily for the first 3 weeks of acute anticoagulation, followed by 20 mg once daily; with warfarin, the target international normalized ratio (INR) is maintained between 2.0 and 3.0. Intermediate-dose anticoagulation was defined as generally 0.5 mg/kg of enoxaparin twice daily or 1 mg/kg of enoxaparin once daily, or an equivalent. This involves dosages lower than the standard dose described above.[19]

Variable definition and outcomes

Patients included in the study are those who exhibited hemoptysis at the time of diagnosing PTE, while those who developed hemoptysis after treatment were excluded. According to the classification method reported in previous studies,[8,20] as well as the severity and daily quantity of hemoptysis, we categorize hemoptysis into three levels: (i) Mild hemoptysis: ≤20 mL/24 h, (ii) Moderate hemoptysis: 20 < volume≤100 ml/24 h, (iii) Massive hemoptysis: >100 mL/24 h. Hemoptysis causes in patient records are classified by the attending physician's round notes into three groups: PTE-related, underlying disease-related, and undetermined causes. If the records do not analyze the cause of hemoptysis, it is determined by two other physicians based on medical records and radiological findings. The clinical outcomes in this study included all-cause mortality, worsening or recurrence of venous thromboembolism (VTE), and deterioration of hemoptysis during hospitalization.

Statistical analysis

Continuous and integral variables were presented as the mean value and standard deviation (SD) for normally distributed variables, and the median and quartile for abnormally distributed variables. Categorical variables were expressed as their counts and proportions. Patients with and without hemoptysis and patients with different causes of hemoptysis were compared by two-sided independent Student's *t*-test for normally distributed variables, Mann–Whitney *U* test for variables obeyed abnormal distribution, and χ^2 test or Fisher's exact test for categorical data. Univariate and multivariate logistic regression analyses were used to identify factors influencing the reduction of anticoagulant dosages. Continuous variables were transformed into binary variables for logistic regression analysis, and the cut-off value was determined by receiver operating characteristic (ROC) curve analysis. Next, the covariates of multivariate analysis were selected from the univariate analysis with statistical significance ($p < 0.1$). Variables with missing values exceeding 10% and collinearity were excluded. Odds ratio (OR) and the corresponding 95% confidence interval (CI) were reported. All tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance. Statistical analysis was conducted using R version 4.2.3.

RESULTS

Comparative analysis of characteristics in PTE patients with and without hemoptysis

Between January 2012 and October 2020, a total of 896 adult patients diagnosed with acute PTE were included, as depicted in Figure 1. Among these cases, 105 patients presented with hemoptysis at the time of PTE diagnosis, resulting in an observed incidence of 11.7%. A comparative analysis of the clinical characteristics between patients with PTE and hemoptysis and those without hemoptysis is detailed in Supporting Information S1: Table 1. Patients with hemoptysis exhibited a male predominance (61.9%) and were of a younger age (48.9 ± 18.5 vs. 59.8 ± 15.8 years; $p < 0.001$) compared to the non-hemoptysis group. The presence of chest pain was significantly higher in the hemoptysis group (41.0% vs. 10.0%; $p < 0.001$), and a greater proportion of patients in this group had a respiratory rate (RR) exceeding 30 breaths per minute ($p < 0.001$). The hemoptysis group showed a lower incidence of elevated right ventricle/left ventricle (RV/LV) ratios. Pulmonary infarction occurred in 17.1% (18/105) of patients in the hemoptysis group, with no significant difference in thrombus location on CTPA between the two groups. Patients with hemoptysis were more likely to have autoimmune diseases (39.0% vs. 16.1%; $p < 0.001$), with a significantly higher prevalence of systemic vasculitis and antiphospholipid syndrome (APS). Additionally, a higher frequency of pulmonary infection (29.5%), primary or metastatic lung cancer (21.0%), and chronic heart failure (16.2%) was observed in the hemoptysis group (Supporting Information S1: Table 1).

Clinical features, disease profile, and anticoagulation patterns in patients with different causes of hemoptysis

We categorized 105 hemoptysis patients into three groups based on the etiology of hemoptysis, as shown

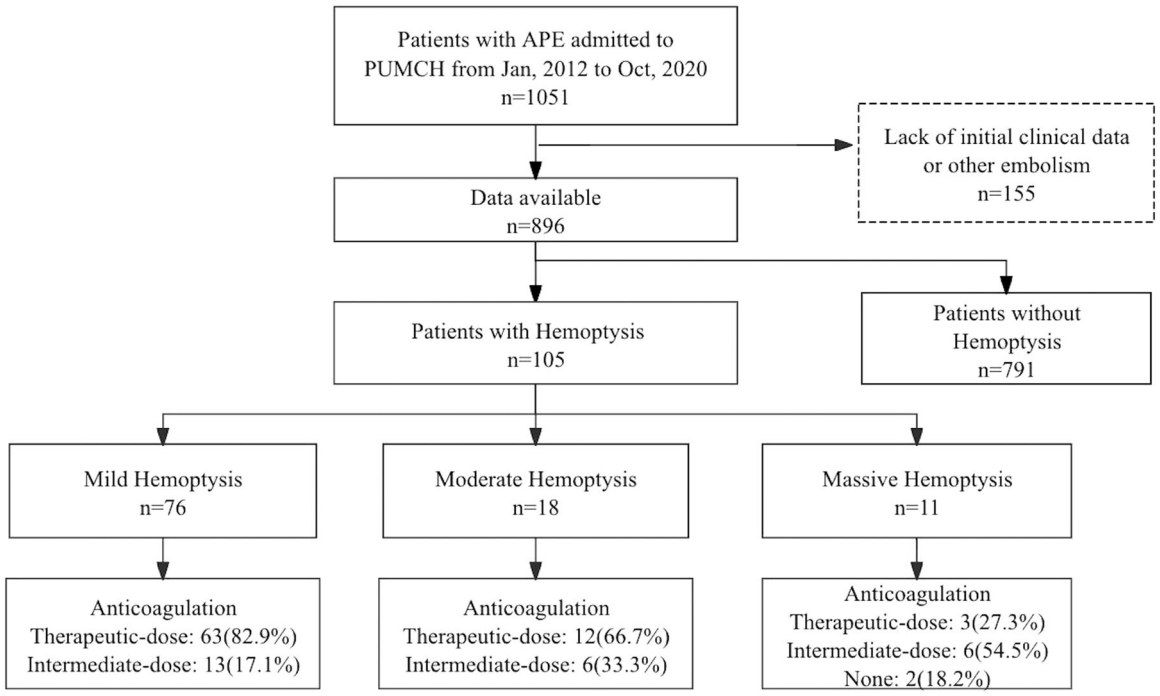

FIGURE 1 Flow chart of study and classification based on volume of hemoptysis. PUMCH, Peking Union Medical College Hospital.

in Table 1. Among them, 54 patients (51.4%) had hemoptysis related to PTE, characterized by elevated median D-dimer levels (5.2 mg/L; $p = 0.009$) (Supporting Information S1: Table 2); 85.2% experienced mild hemoptysis, and 92.6% received therapeutic-dose anticoagulation. Patients with hemoptysis related to underlying diseases accounted for 13.3%, with the highest proportion associated with lung cancer or metastasis (42.9%). In this subgroup, 71.4% experienced massive hemoptysis. Among the three groups, this group had the lowest percentage of patients receiving standard therapeutic-dose anticoagulation, with only 28.6% of patients undergoing this treatment. Additionally, 35.2% of patients presented with hemoptysis of undetermined origin, and 45.9% had concurrent autoimmune diseases. Notably, this group included the highest proportion of patients with systemic vasculitis, accounting for 29.7% of the cohort. Other comorbid diseases, ranked from highest to lowest prevalence, include lung cancer (32.4%), pulmonary infection (27%), and chronic heart failure (13.5%). Moreover, 37.8% of the patients in this group also experienced chest pain, a prevalence second only to those in the PTE-associated hemoptysis group (50%, $p = 0.13$). A total of 64.9% received therapeutic-dose anticoagulation. There were no differences in other laboratory tests, and imaging characteristics among the three groups (Supporting Information S1: Table 2).

Comparative characteristics of patients with different volume of hemoptysis and factors influencing anticoagulation decisions

The volume of hemoptysis was categorized as mild in 76 patients (72.4%), moderate in 18 patients (17.1%), and massive in 11 patients (10.5%). Among patients with different volume of hemoptysis, those with mild hemoptysis had the highest D-dimer levels, with a median of 5 mg/L, while patients with massive hemoptysis had a median D-dimer level of 1.9 mg/L ($p = 0.038$). Regarding other clinical manifestations, although the differences were not statistically significant, the proportions of patients with mild and moderate hemoptysis who experienced chest pain were higher, at 44.7% and 50%, respectively, compared to only 9.1% of patients with massive hemoptysis ($p = 0.06$). There were no differences in vital signs, comorbidities, and PE severity among patients with different volume of hemoptysis. The highest proportion of patients with mild hemoptysis received therapeutic-dose anticoagulation, at 82.9%, whereas only 27.3% of patients with massive hemoptysis were treated with therapeutic-dose anticoagulation, 54.5% received intermediate doses, and 18.2% were not anticoagulated (Table 2). Multivariate logistic regression analysis indicated that the most significant factor influencing the decision of anticoagulation was the presence of massive hemoptysis (Table 3).

TABLE 1 Disease profile, PE severity, volume of hemoptysis and anticoagulation patterns in patients with different causes of hemoptysis.

Characteristics	PTE-related ($n = 54$, 51.4%)	Underlying disease-related (n = 14, 13.3%)	Undetermined causes ($n = 37$, 35.2%)	*P*-value
Comorbid Diseases, *n* (%)				
Chronic Heart failure	8 (14.8)	4 (28.6)	5 (13.5)	0.40
Pulmonary infection	12 (22.2)	7 (50)	10 (27)	0.12
Primary/Metastatic lung cancer	4 (7.4)	6 (42.9)	12 (32.4)	**0.002***
Autoimmune disease	19 (35.2)	5 (35.7)	17 (45.9)	0.57
Antiphospholipid syndrome	10 (18.5)	2 (14.3)	3 (8.1)	0.38
Systemic vasculitis	2 (3.7)	4 (28.6)	11 (29.7)	**0.002***
Hematologic malignancy	1 (1.9)	0 (0)	1 (2.7)	>0.99
PE Risk stratification, *n* (%)				
Low	25 (46.3)	3 (21.4)	12 (32.4)	0.16
Intermediate-low	22 (40.7)	7 (50)	18 (48.6)	0.69
Intermediate-high	6 (11.1)	2 (14.3)	5 (13.5)	0.85
High	1 (1.9)	2 (14.3)	2 (5.4)	0.13
Volume of hemoptysis, *n* (%)				**<0.001***
Mild	46 (85.2)	2 (14.3)	28 (75.7)	
Moderate	7 (13)	2 (14.3)	9 (24.3)	
Massive	1 (1.9)	10 (71.4)	0 (0)	
Anticoagulation patterns, *n* (%)				**<0.001***
Therapeutic-dose	50 (92.6)	4 (28.6)	24 (64.9)	
Intermediate-dose	4 (7.4)	8 (57.1)	13 (35.1)	
None	0 (0)	2 (14.3)	0 (0)	
In-hospital outcomes, *n* (%)				**<0.001***
Death (due to comorbidities)	2 (3.7)	3 (21.4)	7 (18.9)	
Worsening of PTE	0 (0)	0 (0)	1 (2.7)	
Deterioration of hemoptysis	0 (0)	2 (14.3)	0 (0)	

Abbreviation: PTE, pulmonary thromboembolism.

*The difference is statistically significant.

In-hospital outcomes patients with different volume of hemoptysis

During hospitalization, 15 patients experienced mortality, including 2 fatal major bleeding events attributed to worsening hemoptysis, 1 fatal PTE exacerbation, and 12 deaths due to underlying comorbidities (Figure 2).

In patients with mild hemoptysis, 63 patients (82.9%) received therapeutic-dose anticoagulation. However, one patient with underlying lung cancer and intermediate-low-risk PTE succumbed to the progression of PTE and obstructive shock. Additionally, 13 patients (20.3%) received intermediate-dose anticoagulation, and no instances of exacerbation of embolism were observed.

Among patients with moderate hemoptysis, 12 cases (66.7%) received therapeutic-dose anticoagulation, with no cases of worsened hemoptysis. Six patients (33.3%) had anticoagulation reduction, and no instances of PTE progression were observed.

In patients with massive hemoptysis, three cases (27.3%) received therapeutic-dose anticoagulation. Patient 1, a 42-year-old male, had severe influenza virus infection leading to DAH with an intermediate-low risk PTE. Patient 2, a 27-year-old male, had underlying APS-associated DAH with low-risk PTE; neither of these two

TABLE 2 Clinical characteristics, PE Risk Stratification, anticoagulation strategies, and prognosis in patients with different volumes of hemoptysis.

Characteristics	Mild ($n = 76$)	Moderate ($n = 18$)	Massive ($n = 11$)	*P*-value
Male, n (%)	44 (57.9)	11 (61.1)	9 (81.8)	0.32
Age, year, median (IQR)	47 (31,64)	52.5 (34.2,62)	42 (37,68)	0.64
Symptoms, *n* (%)				
Chest pain	34 (44.7)	9 (50)	1 (9.1)	0.06
Dyspnea	45 (59.2)	8 (44.4)	5 (45.5)	0.42
Syncope	3 (3.9)	2 (11.1)	0 (0)	0.28
Signs, *n* (%)				
Pulse ≥ 110 beats/min	10 (13.3)	5 (27.8)	1 (9.1)	0.27
RR > 30 breaths/min	8 (10.7)	2 (11.1)	3 (27.3)	0.30
SBP < 100 mmHg	8 (10.7)	3 (16.7)	1 (9.1)	0.78
SpO_2 < 90%	19 (25.7)	4 (22.2)	3 (27.3)	0.99
Laboratory findings				
WBC ($\times 10^9$/L), median (IQR)	8.4 (5.4,12.4)	9 (5.8,11.2)	7.4 (6.5,10)	0.98
HGB (g/L), mean ± SD	124.3 (21.9)	127.4 (20.5)	122.8 (27.9)	0.83
PLT ($\times 10^9$/L), median (IQR)	188.4 (105.4)	251.1 (96.7)	215.6 (134.1)	0.09
Hypoalbuminemia, n (%)	19 (25)	3 (16.7)	1 (9.1)	0.55
D-dimer (mg/L), median (IQR)	5 (2.4,16.6)	4 (2.1,8.7)	1.9 (1.2,2.8)	**0.038***
cTnI ≥ 0.056 (ug/L), n (%)	14 (21.9)	4 (25)	3 (33.3)	0.67
NT-proBNP (pg/ml), median (IQR)	183 (125,1546)	135(125,484)	164 (125,2078)	0.88
Cr (umol/L), median (IQR)	70 (60,85.5)	76 (62.8,88.2)	75 (58.5,79)	0.75
Echocardiography, *n* (%)				
Elevated RV/LV ratio	9 (16.1)	2 (14.3)	1 (11.1)	0.99
RV-free wall hypokinesis	7 (12.5)	0 (0)	1 (11.1)	0.49
sPAP ≥ 50 mmHg	10 (31.2)	2 (28.6)	2 (50)	0.75
CTPA, *n* (%)				
Central emboli	10 (13.7)	1 (6.2)	0 (0)	0.63
Comorbid diseases, *n* (%)				
Coronary atherosclerotic heart disease	5 (6.6)	2 (11.1)	3 (27.3)	0.07
Cancer	19 (25)	7 (38.9)	3 (27.3)	0.52
Chronic heart failure	13 (17.1)	2 (11.1)	2 (18.2)	0.83
Pulmonary infection	18 (23.7)	6 (33.3)	5 (45.5)	0.25
Primary/metastatic lung cancer	14 (18.4)	4 (22.2)	4 (36.4)	0.36
Autoimmune disease	28 (36.8)	9 (50)	4 (36.4)	0.58
SLE/SS/RA/UCTD/IIM	15 (19.7)	2 (11.1)	0 (0)	0.21
APS	10 (13.2)	3 (16.7)	2 (18.2)	0.73
Systemic vasculitis	10 (13.2)	4 (22.2)	3 (27.3)	0.32
Hematologic malignancy	2 (2.6)	0 (0)	0 (0)	>0.99
Hereditary thrombophilia	1 (1.3)	0 (0)	1 (9.1)	0.23

TABLE 2 (Continued)

Characteristics	Mild ($n = 76$)	Moderate ($n = 18$)	Massive ($n = 11$)	*P*-value
Risk stratification, *n* (%)				
Low-risk	31 (40.8)	5 (27.8)	4 (36.4)	0.59
Intermediate-low-risk	33 (43.4)	9 (50)	5 (45.5)	0.88
Intermediate-high-risk	10 (13.2)	2 (11.1)	1 (9.1)	0.99
High-risk	2 (2.6)	2 (11.1)	1 (9.1)	0.17
Anticoagulation patterns, *n* (%)				**<0.001***
Therapeutic-dose	63 (82.9)	12 (66.7)	3 (27.3)	
Intermediate-dose	13 (17.1)	6 (33.3)	6 (54.5)	
None	0 (0)	0 (0)	2 (18.2)	
In-hospital outcomes, *n* (%)				**0.002***
Survive	70 (92.1)	13 (72.2)	7 (63.6)	
Mortality (due to comorbidities)	5 (6.6)	5 (27.8)	2 (18.2)	
Mortality (exacerbation of PTE)	1 (1.3)	0 (0)	0 (0)	
Mortality (exacerbation of hemoptysis)	0 (0)	0 (0)	2 (18.2)	

Abbreviations: APS, antiphospholipid syndrome; CTPA, computed tomographic pulmonary angiography; IIM, idiopathic inflammatory myopathy; IQR, interquartile range; LV, left ventricle; PTE, pulmonary thromboembolism; RA, Rheumatoid Arthritis; RR, respiratory rate; RV, right ventricle; SLE, Systemic Lupus Erythematosus; sPAP, systolic pulmonary artery pressure; SS, Sjögren's syndrome; UCTD, Undifferentiated connective tissue disease. Elevated RV/LV ratio was defined as dilated RV with basal RV/LV ratio >1.0.

*The difference is statistically significant.

patients underwent dose reduction of anticoagulation, and neither experienced worsening of hemoptysis. Patient 3, a 37-year-old male, had a high likelihood of thrombophilia with protein S deficiency and low-risk PE. Aside from the PTE, no other underlying conditions could explain the hemoptysis, which occurred intermittently. Considering the hemoptysis was caused by PTE, therapeutic-dose anticoagulation was administered and there was no exacerbation of the hemoptysis. Six patients (54.5%) received reduced anticoagulation; among them, two patients with lung cancer faced fatal outcomes attributed to massive hemoptysis and asphyxiation due to worsening hemoptysis. Additionally, two patients (18.2%) with Behçet's disease and pulmonary artery aneurysms did not receive anticoagulation. Following active treatment of the primary disease, their hemoptysis was alleviated without exacerbation (Figure 2).

DISCUSSION

The literature reports an occurrence rate of hemoptysis ranging from 2.6% to 7.6%.[2–4] In our study, the incidence of hemoptysis was 11.7%, slightly higher than the reported international rates. This discrepancy may be attributed to the composition of our study population, consisting of hospitalized patients with a higher burden of comorbidities compared to the emergency department. Our research identified a higher propensity for concurrent chest pain, and a lower severity of PTE, with a higher proportion of patients scoring 0 on the sPESI. Additionally, the hemoptysis cohort displayed lower levels of NT-proBNP and a reduced incidence of elevated RV/LV ratio. Hemoptysis accompanied by chest pain and pulmonary infarction is considered to reflect the characteristics of peripheral PTE,[21,22] where blood stasis and hypoxia at the site of embolism contribute to pulmonary tissue edema and extravasation, leading to hemoptysis.[23] This, to some extent, elucidates the relatively lower severity of PTE and fewer intermediate-high-risk and high-risk PTE patients observed in the hemoptysis cohort.

In the realistic clinical scenario, identifying the etiology of hemoptysis in patients with acute PE poses a considerable challenge. Acute PTE can lead to hemoptysis, typically due to blood stasis at the embolism site, causing pulmonary tissue edema and extravasation of blood. It is primarily characterized by blood-tinged sputum and mild hemoptysis,[23] but recent reports have also documented cases of acute PTE accompanied by

TABLE 3 Univariate and multivariate logistic regression analysis of factors influencing the anticoagulation strategies.

	Univariate analysis			Multivariate analysis		
Characteristic	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***p*-value**
Dyspnea	1.47	0.61–3.54	0.39			
Chest pain	1.31	0.53–3.23	0.55			
Central embosis	0.64	0.17–2.39	0.51			
PLT	1.00	1.01–1.02	0.90			
PLT < 100× 10^9/L	0.77	0.26–2.29	0.64			
Age	1.02	0.99–1.04	0.14			
Age >68 years old	2.56	0.9–7.28	0.07	2.48	0.81–7.61	0.113
Lung cancer or metastatic lung cancer	0.52	0.19–1.42	0.20			
Hematologic malignancies	0.34	0.02–5.59	0.45			
Surgery or trauma within 3 months	0.65	0.2–2.1	0.47			
Low-risk PE	1.32	0.53–3.31	0.56			
Intermediate-low-risk PE	0.83	0.35–2	0.68			
Intermediate-high-risk PE	1.18	0.3–4.64	0.82			
High-risk PE	0.50	0.08–3.17	0.46			
Mild hemoptysis	0.22	0.09–0.57	**0.002***			
Moderate hemoptysis	1.57	0.53–4.7	0.42			
Massive hemoptysis	10.53	2.55–43.51	**0.001***	10.31	2.45–43.48	**0.001***

Abbreviations: Cl, confidence interval, OR, odds ratio.

*The difference is statistically significant.

massive hemoptysis.[12] A retrospective study in France revealed that approximately 50% of hemoptysis cases were idiopathic, with no identifiable cause.[24] In our study, we faced challenges in determining whether hemoptysis originated from the PTE itself or from concurrent underlying diseases in 35.2% of patients. Therefore, this article outlines the comorbidities of such patients.

Which comorbidities are more prevalent in PTE patients presenting with hemoptysis? A study on PTE with hemoptysis indicated that among 127 patients with acute PTE and hemoptysis, associated diseases included lung cancer (29.9%), pulmonary tuberculosis (8.7%), bronchiectasis (5.5%), pulmonary aspergillosis (2.4%), pulmonary arteriovenous malformation (0.8%), and microscopic polyangiitis (0.8%).[8] In our study, we identified autoimmune diseases, primary or metastatic lung cancer, pulmonary infection, and chronic heart failure as the most common comorbidities in patients with hemoptysis. Hemoptysis can result from direct invasion of blood vessels by lung malignancies or infectious lesions, or from the rupture of bronchial arteries caused by pulmonary lesions associated with tissue necrosis or inflammation.[25,26] Patients with chronic heart failure exhibit an increased propensity for hemoptysis due to prolonged pulmonary congestion and edema.

Patients with autoimmune diseases often experience an active state of their immune disorder during hospitalization, leading to a higher incidence of VTE compared to inactive states. In this study, vasculitis was most prevalent among autoimmune diseases, with 37.5% had ANCA-associated vasculitis (AAV), 25% had Behçet's disease, 12.5% had Takayasu arteritis, and 25% had unclassified vasculitis. Hemoptysis may occur due to direct vessel wall damage caused by the infiltration of inflammatory cells, resulting in the loss of vascular integrity and subsequent bleeding.[9,27] Hemoptysis is frequently encountered in vasculitis with different types, making it challenging to differentiate. In Behçet's disease, up to 40% of patients may present with vascular lesions, with pulmonary aneurysms and hemoptysis being the most common symptoms.[28–30] In Takayasu arteritis, thickening and stenosis of the pulmonary artery wall may lead to hemoptysis in approximately half of the patients with pulmonary artery involvement.[31,32]

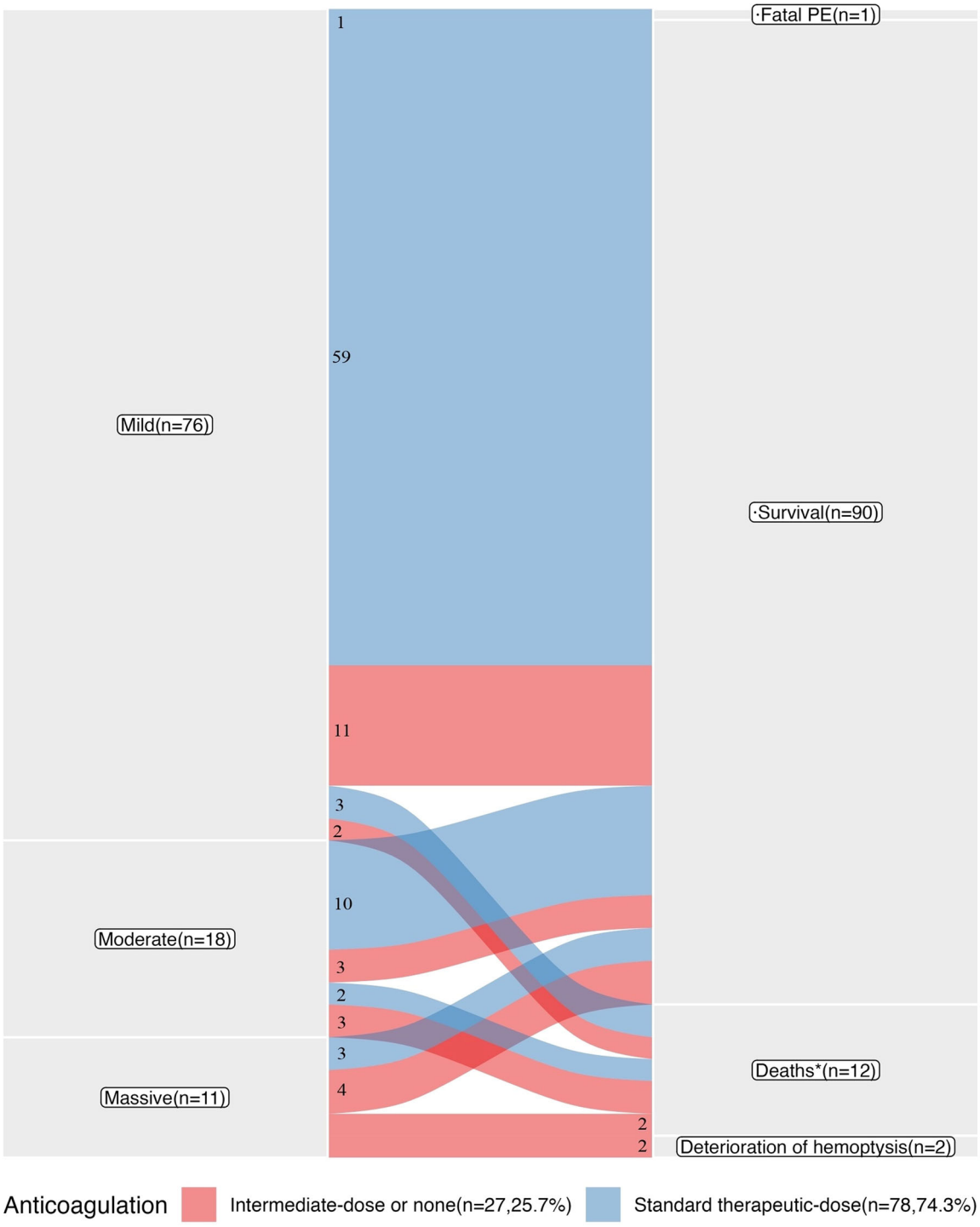

FIGURE 2 Classification, anticoagulation managements and outcomes of the three groups (Deaths*, due to underlying comorbidities.).

In AAV, besides presenting with occasional mild hemoptysis, DAH can manifest as massive hemoptysis or remain subtle, initially appearing as mild hemoptysis. Hemoptysis in patients with APS is possibly associated with the high incidence of PLT reduction.[33] Other connective tissue diseases (CTD) may also exhibit pulmonary involvement, leading to interstitial changes, small vessel vasculitis, and occasionally mild hemoptysis.

We propose a prioritized approach for managing such cases. Firstly, for patients with a clear underlying disease, which might be one of the causes of hemoptysis, aggressive treatment of the primary disease is essential. In our study, the causes of hemoptysis in 51 patients were attributed to underlying diseases or remained undetermined, of which 22 cases (43.1%) involved comorbid autoimmune diseases. In such cases, active

treatment targeting the underlying disease is crucial. For patients with Behçet's disease presenting with both pulmonary aneurysms and PTE, the mechanism of thrombosis is primarily related to systemic inflammation of the vessel wall rather than abnormal coagulation function. Currently, it is believed that treatment for vasculitis should take precedence over anticoagulation, and most patients' thrombosis improves without the need for anticoagulation after controlling the primary disease.[34–36] In our study, two BD patients with concomitant pulmonary aneurysms had hemoptysis volumes exceeding 100 mL and did not receive anticoagulation. After the addition of glucocorticoids and immunosuppressive therapy to control the primary disease, hemoptysis associated with PTE improved. Tseng et al. reported and reviewed five cases of vasculitis patients with PTE and DAH.[15] All patients received glucocorticoids and immunosuppressive agents, with 60% undergoing plasmapheresis. There were no episodes of hemoptysis or exacerbation of embolism during follow-up after the primary disease improved. In our study, patients with autoimmune diseases received simultaneous active treatment for their underlying diseases. For instance, a patient with Takayasu arteritis, when administered Tocilizumab (Anti-IL-6 receptor monoclonal antibody) in conjunction with therapeutic-dose anticoagulation, achieved stabilization of both the underlying disease and hemoptysis and no recurrence of thrombosis.

Moreover, multivariate logistic regression analysis revealed that the volume of hemoptysis is a significant factor influencing clinicians' anticoagulation decisions, aligning with clinical experience. Secondly, balancing the volume of hemoptysis with the severity of PTE allows for the appropriate management of the most critical aspect. Patients with massive hemoptysis have a poorer prognosis and present greater clinical challenges due to their higher overall severity. In such cases, considering necessary interventional measures might be required. Among patients with massive hemoptysis, six (54.5%) received reduced-dose anticoagulation. Nevertheless, two patients with lung cancer still faced fatal outcomes due to massive hemoptysis and asphyxiation from worsening conditions. Additionally, one lung cancer patient underwent bronchial artery embolization (BAE) followed by initial treatment with a continuous heparin infusion. Post-BAE, the patient's condition improved, transitioning to therapeutic-dose LMWH anticoagulation. Subsequently, there was no further exacerbation of hemoptysis or progression of PTE. However, the patient ultimately succumbed to the worsening of the underlying malignancy. Initiating BAE followed by the recovery of therapeutic-dose anticoagulation, as suggested in previous reports,[14,37,38] or employing interventional approaches instead of traditional anticoagulation strategies,[39,40] can be beneficial in managing such complex scenarios.

This study is limited by its single-center retrospective design, and the recorded hemoptysis volume is based on medical record documentation, which may differ from the actual volume. Moreover, our center has a relatively high proportion of rare and complex diseases. Since the study focuses on hospitalized patients, the findings may have limited applicability to the outpatient setting due to differences in disease spectrum. However, research on acute PTE with hemoptysis is scarce. Our study supplements the clinical features and comorbidity spectrum, offering new insights for the treatment strategy analysis of such patients.

CONCLUSIONS

The occurrence of hemoptysis in hospitalized patients with acute PTE was 11.7%. This patient population frequently presented with chest pain and had a relatively higher likelihood of comorbidities such as autoimmune diseases, lung cancer or metastatic lung cancer, pulmonary infection and chronic heart failure. The etiology of hemoptysis is multifactorial; a significant proportion remains undetermined. Rigorous screening and active treatment of underlying diseases that could potentially cause hemoptysis are crucial in these patients. Actively managing potential underlying causes of hemoptysis, such as autoimmune diseases, can be beneficial. Additionally, massive hemoptysis significantly influences anticoagulation decision-making and is associated with poor outcomes. In facing complex clinical decisions, it is essential to balance the volume of hemoptysis with the risk stratification of PE, considering necessary interventional measures might be required.

GUARANTOR

Dr. Juhong Shi acts as the guarantor for this manuscript and accepts full responsibility for the work, ensuring that the integrity and accuracy of the research are maintained. Dr. Juhong Shi confirms that all authors have seen and approved the final version of the manuscript and have agreed to its submission for publication.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: Yiyao Li, Juhong Shi. *Collected data*: Yiyao Li, Peijun Xue. *Analysed the data:* Yiyao Li, Peijun Xue. *Interpreted the results*: Yiyao Li, Ting Zhang, Min Peng, Xuefeng Sun, Juhong Shi. *Wrote*

the first draft of the manuscript: Yiyao Li, Juhong Shi. *Contributed to the writing of the manuscript*: Yiyao Li, Peijun Xue, Ting Zhang, Min Peng, Xuefeng Sun, Juhong Shi. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval was obtained from the Institutional Review Board of the Peking Union Medical College Hospital (Ethical review number: B164). Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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