

DIFFERENCES IN PULMONARY AND EXTRA-PULMONARY CAUSES OF HEMOPTYSIS

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ABSTRACT

Background: Hemoptysis is the coughing up of blood from the tracheobronchial tree. Hemoptysis is most often a manifestation of lung diseases. The etiology of hemoptysis can also be extra-pulmonary. A certain number of cases are idiopathic. The gold standard in the diagnosis is computed tomography, pulmonary angiography, and aortography. The treatment of hemoptysis is the treatment of the underlying disease and, if necessary, bronchoscopy.

Methodology: This study examines 235 patients presenting with hemoptysis at the Emergency Center of Serbia, University Clinical Center, focusing on demographics, comorbidities, diagnostic procedures, and treatment outcomes. Patients underwent thorough clinical evaluation and laboratory tests, with an emphasis on distinguishing pulmonary from non-pulmonary causes. Descriptive and inferential statistics were employed to analyze the data, revealing significant findings.

Results: Results showed a male predominance (62.1%) with an average age of 60.9 years. Comorbidities, particularly arterial hypertension, were prevalent. Chest imaging, including X-rays and CT scans, aided in diagnosing conditions such as pulmonary thromboembolism and malignancy. Logistic regression highlighted predictors for outpatient treatment, including higher hemoglobin levels and non-pulmonary etiology. Bronchoscopy was performed in 23.8% of cases, revealing varied findings, including active bleeding, inflammation, and bronchiectasis. Notably, uncontrolled arterial hypertension emerged as a leading cause of hemoptysis. Patients with pulmonary causes exhibited distinct clinical and laboratory profiles compared to those with non-pulmonary etiologies.

Conclusion: This study underscores the heterogeneity of hemoptysis etiologies and the critical role of thorough evaluation in guiding treatment decisions. Understanding the differences in clinical characteristics and laboratory results between pulmonary and non-pulmonary causes informs optimal management strategies and balancing outpatient vs. inpatient care.

Keywords: hemoptysis, non-pulmonary etiology, comorbidity

INTRODUCTION

Hemoptysis is the coughing up of blood from the tracheobronchial tree. Blood can be from the pulmonary or bronchial circulation (1). The severity varies from trace to massive bleeding, representing a life-threatening condition that requires immediate diagnostic and treatment (1). Massive hemoptysis are defined by an amount greater than 200 ml of fresh blood coughed up. If we are talking about massive hemoptysis, we must mention that they have a high mortality rate, up to 38% (2).

Hemoptysis is most often a manifestation of lung diseases such as lung cancer, foreign body aspiration, abscess, granulomatosis, bronchiectasis, pulmonary thromboembolism, and pulmonary tuberculosis (3). The most frequent pulmonary causes are pneumonia or respiratory infections. According to research by Kaur and college still about 60% of respiratory bacterial pathogens cause is *Mycobacterium tuberculosis*. In addition, less frequent was *Pseudomonas* infection, *Klebsiella* or *E.colli* (4). Approximately 19% of patients with lung cancer present with hemoptysis (5). In the study by Hert et al., a quarter of patients with malignancy presented with coughing blood had a

normal chest radiography (6). Therefore, patients with recurrent hemoptysis and a negative radiography finding should be referred to further diagnostic methods (chest CT scan, bronchoscopy). That is the reason that we need a lung cancer screening plan. The etiology of hemoptysis can also be extra-pulmonary. It can be unregulated arterial hypertension, overdose of anticoagulants, cardiac decompensation, changes in the vocal cords, endometriosis, and many others (1,7). Uncontrolled high blood pressure can contribute to the development of hemoptysis in patients with unidentified causes of hemoptysis and, also may be a risk factor for bleeding of other organs - intracerebral hemorrhage, retinal hemorrhage, or epistaxis (8). However, a certain number of cases, even up to 50% according to some literature data, are idiopathic, without a clear cause on radiography or bronchoscopy (9).

Any expectoration of blood requires a detailed diagnosis that includes clinical examination, sputum analysis, radiology methods of visualization, or bronchoscopy. The gold standard in the diagnosis of hemoptysis is computed tomography (CT scan), pulmonary angiography, and aortography to identify the arteries that are the source of bleeding (8). A chest CT scan must be performed in all patients with pronounced hemoptysis, suspected bronchiectasis, excavation, or infiltrative changes suspicious for lung cancer. Angiography is a non-invasive radiological technique that can determine the presence and origin of the bleeding source (8,10).

The treatment of hemoptysis is the treatment of the underlying disease that led to their appearance. The most common treatment is conservative with hemoptysis, diuretics or antibiotics, depending on the cause (1). Treatment is about seven to ten days. In the case of massive hemoptysis, bronchoscopy can first isolate the bleeding site, define the cause (exploration or biopsy) and be the primary modality of treatment (1). Treatment of life-threatening hemoptysis is based mainly on a surgical approach or bronchial artery embolization (11). Artery embolization is complete cessation of hemoptysis and varied from 70%-99%. However, the recurrence rate is still high, from 10% to 57%. Causes for that can be incomplete initial embolization, recanalization or new collaterals (12).

There is a lack of literature data about the etiology of hemoptysis regarding the spectrum of disorders that present with this symptom. Because of that, this study has the goal of determining the clinical profile of hemoptysis and its correlation with radiological findings. The aim of this retrospective study is to determine the etiology of hemoptysis and see differences in pulmonary and extra-pulmonary etiology.

MATERIAL AND METHODS

The study included 235 patients who were examined in the Emergency Center of Serbia, University Clinical Center of Serbia, due to verified hemoptysis.

Hemoptysis is defined as coughing up blood from the lungs or tracheobronchial tree. They are classified into non-massive and massive according to the amount, while massive implies an amount over 200 ml per day¹³. The presence and amount of bloody sputum were verified for each patient in the pulmonology observation room of the Emergency Center on the day of the examination. All patients were clinically evaluated with a detailed history. The following data were collected from the available medical records: age at the time of diagnosis of hemoptysis, gender, smoking status, presence of comorbidities, previously diagnosed lung disease or malignancy, therapy, duration of hemoptysis and other symptoms. If patients have two potential

causes of hemoptysis, we have a multidisciplinary approach to a final diagnosis with more laboratory and diagnostic procedures. Some patients were excluded if we did not have a final diagnosis because of the intertwining of several factors that did not give us a clear cause even after extensive diagnostics.

All subjects underwent a physical examination, including measurement of blood pressure, heart rate, and oxygen saturation, as well as auscultation of the lungs and heart.

Laboratory analyses included blood count, C reactive protein (CRP), INR, and D dimer analyses. The cutoff value for D dimer was 0.5 mg/L and for CRP 5 mg/L.

All patients underwent a chest X-ray, and according to indications, a chest CT scan was performed for a certain group of patients in order to confirm or exclude pulmonary thromboembolism, malignancy, or consolidation.

Statistical analysis: Statistical analysis were performed using the statistical program SPSS (V 23.0, IBM Corp., Armonk, NY, USA, 2019). Descriptive statistical methods, statistical hypothesis testing methods and dependency testing methods are used to analyze primary data. Of the descriptive statistical methods, central tendencies (arithmetic mean, median, mode), measures of variability (interval of variation, standard deviation and interquartile range) and relative numbers were used. Methods for testing statistical hypotheses include *t*-test and analysis of variance. Statistical hypotheses were tested at a statistical significance level (alpha level) of 0.05.

RESULTS

The study included 235 patients examined in the Emergency Center between April 2022. and April 2023. due to verified hemoptysis. The average age of the patients was $60,9 \pm 18,6$ years (range from 18 to 91 years). About two thirds of the patients were male (62.1% vs. 37.9%). The distribution of comorbidities is presented in Table 1. 27% of all patients did not have any comorbidity.

The average systolic arterial blood pressure was 140 mmHg (80-220), and the diastolic 81 mmHg (50-121). The average value of hemoglobin was 127 g/L, and anemia was detected in 67 patients (28.5%). The average number of platelets was 232/nL, thrombocytopenia was noted in 15 (6.4%) patients. Decreased concentration of D-dimer was observed in 84 (35.7%) and INR was seen in 14 patients (5.9%). Decreased values of CRP were detected in 79 patients (70.5%). There was no correlation with elevated values of D dimer and pulmonary embolism CT findings.

The median duration of hemoptysis before examination is 2 days (Figure 1). Thirty patients (12.7%) had massive hemoptysis.

Oral anticoagulants were taking 47 (20%) patients. 89 patients (37.9%) need hospitalization due to hemoptysis. Results of multiple logistic regression for predicting the possibility of outpatient treatment in patients with hemoptysis were presented in Figure 2. A statistically significant predictor of the decision for outpatient treatment were higher hemoglobin value ($p < 0.001$) and non-pulmonary etiology of the disease ($p = 0.008$), so patients with anemia need hospital treatment and in some percent transfusion.

Embolization was performed in 3 patients (1.30%). Fifty-six patients (23.8%) underwent bronchoscopy: 30.4% had normal endoscopic findings and signs of infiltration, signs of inflammation 26.6%, active bleeding 6.3%, coagulum 3.8%, foreign body (mostly food) 2.5%. Of the 6 patients who had active bleeding on bronchoscopy, the etiology of the bleeding was not

clarified in one, pneumonia was proven in one, bronchiectasis was caused in three, and malignant lung disease was seen in one.

In 7.6%, the findings were completely normal without any pathological findings. The same number of patients had confirmed progression or de novo described lung malignancy and unregulated arterial blood pressure (17.8%). Pneumonia as the main diagnosis was in 20 patients, and the same with bronchiectasis, 14 arterial heart failure or pulmonary embolism (PE), 10 active tuberculosis or oral anticoagulant overdose, 9 bronchitis, 6 atelectasis due to foreign body (food), 5 or fewer patients had glottis or neck carcinoma, COVID pneumonia, vasculitis, deposits in lung, gastroesophageal reflux disease. Pulmonary cause was in 55.1% and non-pulmonary in 44.9%. Interesting was that the main individual cause in all study populations (pulmonary or not) was unregulated arterial blood pressure in 17.8%. All definitive diagnosis/cause of hemoptysis presented on Figure 3.

Patients with pulmonary vs. non-pulmonary causes of hemoptysis differed in the concentration of D-dimer and CRP, presence of anemia, values of systolic, and diastolic arterial blood pressure, as well as in the duration of hemoptysis before hospitalization.

Patients with non-pulmonary etiology more often had pre-existing arterial hypertension and less frequently had pre-existing obstructive lung disease. Also, patients with pulmonary problems more often had anemia and elevated CRP concentrations as well as elevated D-dimer concentrations. They did not differ in the volume of hemoptysis. Results presented in Table 2.

DISCUSSION

With this research, we wanted to emphasize the importance of hemoptysis as a symptom that we see in everyday practice and that presents us with a big dilemma in diagnosis, treatment, and final outcome.

In addition to extensive diagnostics, a larger percentage of patients remain without a final diagnosis, i.e., a discovered cause for the occurrence of hemoptysis. In a study by Park and colleagues that included more than 1,000 subjects, about 5.7% of patients had an undiagnosed cause for hemoptysis (13). We had a similar percentage compared to those previous studies, our 18 patients (7.6%) remained without a diagnosis, even though they were treated conservatively and did not repeat. The reason for the small number of patients with an unexplained etiology is probably because in the Emergency Center of Serbia, different types of diagnostics are more available in one place and immediately, in the form of laboratory analyses, chest CT scans, bronchoscopy, surgery, interventional radiology, a multidisciplinary approach of a high number of specialists in one place, which contributed to the identification of the cause in almost all patients. According to data from previous studies, coughing of blood occurs most often in older patients, while the prevalence in the pediatric group is significantly smaller. The results of the meta-analysis by Ittrich and colleagues match with our results (14). The average age is almost the same around 60 years. Only 2 patients were of adolescent age and the male gender was more dominant as in their study. The predominance of older age could be explained by the influence of lifestyle, longer smoking status, and the existence of comorbidities that can also be the cause of hemoptysis (mitral stenosis, heart failure), while in children the cause of hemoptysis is mainly related to aspiration of a foreign body or congenital anomalies (15). They are significantly less common in children, but they can also be equally extensive and life-threatening.

As we mentioned, elderly patients usually have at least one of the comorbidities. According to our results, the majority of patients had arterial hypertension as the dominant comorbidity. However, the most common final individual diagnosis after diagnostic was extra-pulmonary cause - unregulated arterial hypertension (17.8%) and not lung disease. It is probably due to the high pressure in the systemic circulation, the bronchial circulation is responsible for about 90% of hemoptysis (13,16). In the study by Moua and colleagues, the impact of antihypertensive drugs was examined in patients with cystic fibrosis who have chronic inflammation of the airways and frequent bleeding from the bronchial arteries (16). It has been proven that reducing the pressure in the systemic and therefore the bronchial circulation can prevent recurrent hemoptysis in patients with cystic fibrosis who generally have a high tendency to bleed. In this way, bleeding is regulated as part of an increase in blood pressure in patients with bronchiectasis, as bleeding from the bronchial arteries has been proven in them. Since the bronchial arteries are responsible for hemoptysis in these patients, which can be massive, recurrent, and often do not respond to conservative treatment with hemostyptics, bronchial artery embolization (BAE) is the most common type of final solution. It was first introduced in 1973. and since then the technique has improved significantly, the rate of immediate bleeding control to >70% (17). This is a significant type of treatment if we know that according to the literature, even conservatively treated massive hemoptysis has a mortality rate of 50 to 100%. In our study, 3 patients underwent embolization and hemoptysis was caused by bronchiectasis due to the sequelae of pulmonary tuberculosis, and the patients fully recovered. It is known that uncontrolled hypertension can be a risk factor for bleeding in other organs: intracerebral bleeding, epistaxis, intraocular bleeding, etc. None of our patients had any of the those types of bleeding.

Although the dominant cause of hemoptysis was extra-pulmonary, more than half of the patients had some pulmonary cause of hemoptysis. The most common cause was lung cancer, 11 were newly diagnosed and underwent an urgent bronchoscopy with PH verification. Unfortunately, due to non-specific symptoms for lung cancer such as fatigue or cough, which our patients justify by smoking, hemoptysis is often a signal for radiological diagnosis when the existence of a lung tumor can be shown, and unfortunately often at an advanced stage (18,19). For this reason, there should be lung cancer screening for those over 40 years and smokers, that is not still in our country regulated by the government. Bleeding occurs due to the infiltration of blood vessels by tumor cells, tumor necrosis and obstruction of blood vessels, and increased pressure in the systemic circulation (18,19). Sometimes emergency bronchoscopy is needed to stop bleeding locally, as was done in 6 patients.

We found very significant differences between clinical characteristics in patients with pulmonary or non-pulmonary causes. Patients with pulmonary the main cause of hemoptysis had longer duration of coughing blood, a greater percentage of anemia, higher values of d dimer and CRP, and a need for bronchoscopy. That is in accordance with the reason for hemoptysis: CRP was higher because of pneumonia, D dimer because of the percentage patients with PE, and anemia with cancer bleeding. But patients with non-pulmonary reasons for hemoptysis had higher values of systolic and diastolic pressure that are in line with our final results, as the main single dominant reason for hemoptysis was untreated arterial hypertension.

Statistically significant predictors of the decision for outpatient treatment were higher hemoglobin value and non-pulmonary etiology of the disease. So, patients with anemia need hospital treatment

and, in some percent, transfusion. Explanation for non-pulmonary pathology can treat outpatients because was less massive hemoptysis in this group, less content and a non-life-threatening clinical course, they had a good response to diuretics or antibiotics. In contrast, massive hemoptysis had to be treated in the hospital. Up to 15% of cases of hemoptysis are life-threatening, and need urgent life-saving intervention and in our case, 6.3% have active bleeding and need urgent bronchoscopy (20,21). About a third of patients required hospital treatment for hemoptysis. Patients with pneumonia, bleeding tumors, massive hemoptysis, proven tuberculosis, and pulmonary thromboembolism had to be treated in the hospital at the Clinic for pulmonology or because of unregulated INR and heart failure at the Clinic for cardiology.

CONCLUSIONS

Hemoptysis can be life-threatening and lead to a fatal outcome. That is why timely and adequate diagnosis and treatment are needed. Identification of the etiology is essential for the efficient management of hemoptysis. The seriousness of hemoptysis is supported by the fact that a third of the patients required emergency hospital treatment. Although hemoptysis is considered to have pulmonary origin, it has been proven that there are a large number of extra-pulmonary causes of the same. As we proved, there are significant differences in duration, clinical characteristics, and laboratory results that guide us when deciding on outpatient or hospital treatment. So we need a multidisciplinary approach for right treatment and no time is wasted on inadequate referral to a pulmonologist without an adequate medical history and examination.

LITERATURE:

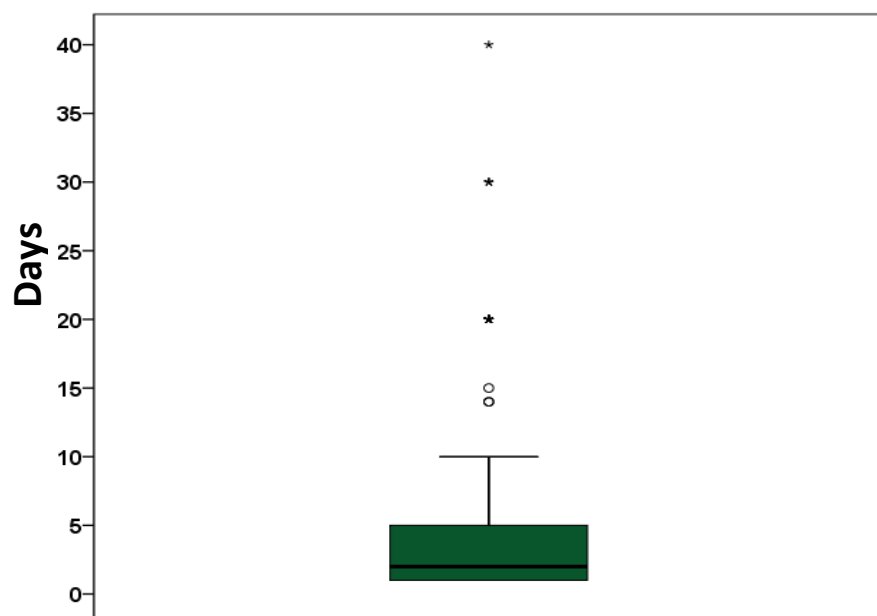
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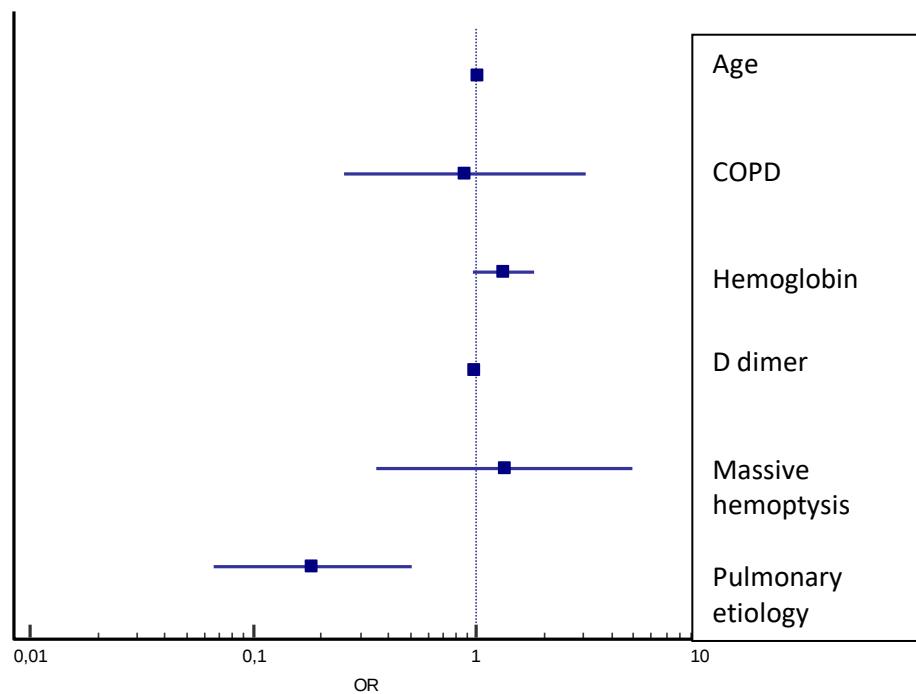
Table 1- Distribution of comorbidities.

Comorbidity	N (%)
Arterial hypertension	113 (48.1)
COPD or asthma	36 (15.3)
Coronary artery disease	27 (11.5)
Diabetes mellitus	25 (10.6)
Atrial fibrillation	23 (9.8)
Malignancy	13 (5.5)
Hypothyroidism	9 (3.8)
Cerebrovascular disease	8 (3.4)
Psychiatric disease	5 (2.1)
Gastric disease	5 (2.1)
Renal disease	3 (1.3)
Thrombosis	3 (1.3)
Heart valve disease	1 (0.4)

Graphic 1. Duration of hemoptysis



Graphic 2. Results of multiple logistic regression for predicting the possibility of outpatient treatment in patients with hemoptysis



Graphic 3. Final diagnosis for cause of hemoptysis

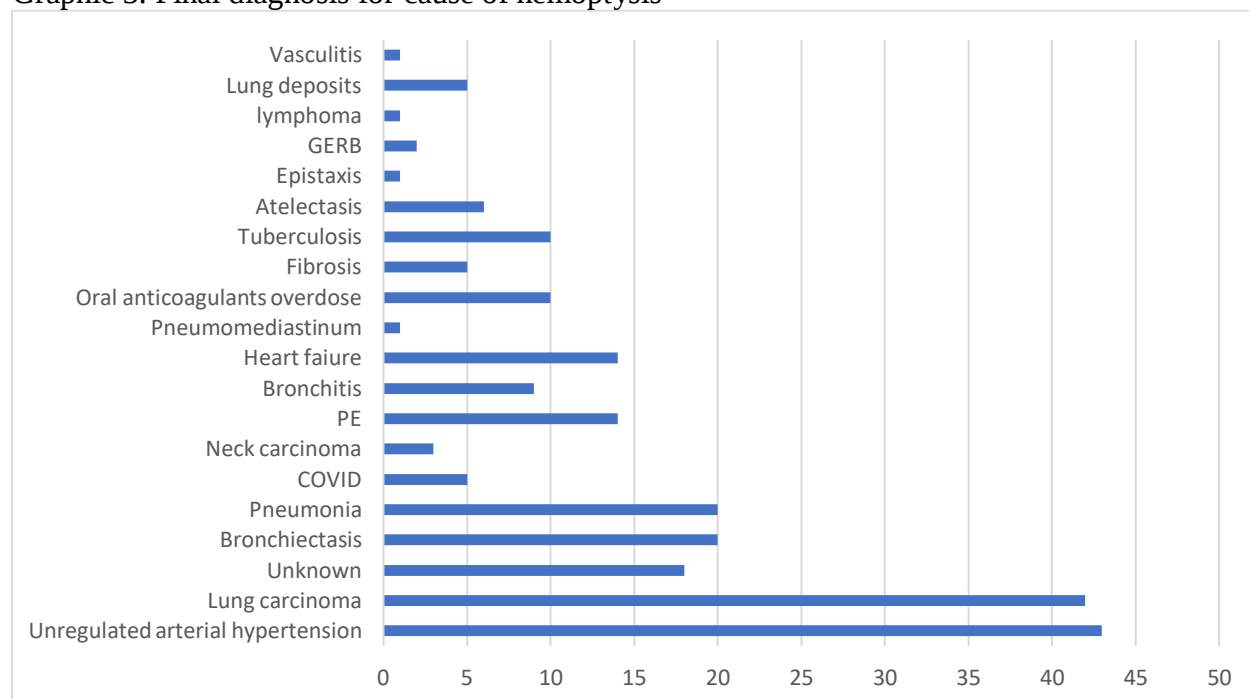


Table 2 - Characteristics of patients with pulmonary and non-pulmonary pathology

Characteristics	Pulmonary	non-pulmonary	p
N (%)	133	102	
Male (%)	79 (59,4)	67 (65.7)	0.33
Age (years)	66 (17 – 91)	65,5 (20 – 90)	0.38
Duration fo hemoptysis (days)	8 (1 – 180)	6 (1 – 365)	0.017
Systolic arterial preassure (mmHg)	130 (80 – 200)	145 (100 – 220)	0.009
Diastolic arterial preassure (mmHg)	80 (50 – 121)	90 (50 – 119)	0.008
Arterial hypertension, n (%)	56 (43)	57 (55.9)	0.04
COPD, n (%)	30 (22.6)	6 (5.9)	<0.001
Oral anticoagulants, n (%)	24 (18)	23 (22.5)	0.39
Hgb (g/L)	124,5 (54 – 166)	133 (89 – 176)	0.08
Anaemia	48 (57.1)	19 (37.3)	0.03
Platelets (n/nL)	236 (41– 691)	231 (85 – 462)	0.34
Thrombocytopenia, n (%)	9 (6.1)	6 (5.9)	0.79
INR	1.03 (0.87 – 13.6)	1.07 (0.44 – 12.1)	0.3
Increased INR, n (%)	9 (6.1)	5 (5.2)	0.72
D-dimer (mg/L FEU)	1.03 (0.17 – 30.8)	0.5 (0.14 – 6.55)	0.001
Decreased D-dimera	59 (44.3)	25 (24.5)	0.009
CRP	33.2 (0.6 – 475)	5.3 (0.6 – 107)	<0.001
Decreased CRP	60 (45.1)	19 (18.6)	0.01
Massive hemoptysis	18 (13.5)	12 (11.7)	0.53
Bronchoscopy, n (%)	45 (33.8)	11 (10.8%)	0.09