Int J Clin Exp Med 2019;12(4):4154-4160
www.ijcem.com /ISSN:1940-5901/IJCEM0084469

Original Article

The predictive value of C-reactive protein for endobronchial, biopsy-induced bleeding in patients with lung cancer

Sai-Bin Wang[1], Jun-Wei Tu[1], Yue-Xiang Shui[2], Shun-Jin Zhao[2]

[1]*Department of Respiratory Medicine, Jinhua Municipal Central Hospital, Jinhua 321000, Zhejiang Province, China;* [2]*Department of Respiratory Medicine, Lanxi People's Hospital, Lanxi 321100, Zhejiang Province, China*

Received August 22, 2018; Accepted January 7, 2019; Epub April 15, 2019; Published April 30, 2019

Abstract: Endobronchial biopsy (EBB)-induced bleeding occurs commonly in patients with lung cancer, but effective biomarkers for the prediction of EBB-induced bleeding remain unknown. The levels of C-reactive protein (CRP) that may be associated with EBB-induced bleeding have never been examined. Here, we conducted a retrospective study using 577 consecutive patients with lung cancer who underwent EBB between January 2014 and February 2018 at a tertiary hospital. The association of preoperative serum CRP levels with the risk of EBB-induced bleeding was tested using multivariate regression analysis adjusted for demographics, tumor characteristics, and comorbidities. The incidence of EBB-induced bleeding was 37.8%, and we found that the mean serum CRP level was significantly higher in the bleeding group than in the non-bleeding group ($P < 0.001$). In the multivariate regression analysis using quartiles of CRP levels, compared to Q1, the odds ratio (95% confidence interval [CI]) of Q2, Q3, and Q4 were 3.213 (1.760, 5.865), 3.069 (1.657, 5.686), and 6.434 (3.402, 12.168) after adjustment for potential confounding risk factors, respectively. Higher levels of CRP were related to a higher incidence of EBB-induced bleeding events (P for trend < 0.0001). In addition, the area under the receiver operating characteristics curve, with a cutoff value of 1.15 mg/L, was 0.692 (95% CI: 0.657, 0.739). In conclusion, preoperative serum CRP was an independent risk factor for EBB-induced bleeding in patients with lung cancer, suggesting its possible role as a useful biomarker for predicting the risk of EBB-induced bleeding.

Keywords: C-reactive protein, lung cancer, endobronchial biopsy, bleeding, prediction

Introduction

Hemorrhage is a common complication for bronchoscopists during bronchoscopy, especially when a biopsy is performed, and a massive hemorrhage could be life-threatening [1, 2]. Endobronchial biopsies (EBBs) are widely used in the histopathological diagnosis of airway disorders [3].

Patients with lung cancer are the main individuals who need bronchoscopies and EBBs. Several risk factors have been proposed for hemorrhage during bronchoscopy, including thrombocytopenia, anti-coagulant or anti-platelet therapy, immunosuppression, severe liver and kidney disease, mechanical ventilation, pulmonary arterial hypertension, and bleeding tendencies [4-7]. However, there is no recommended biomarker to date for the prediction of EBB-induced bleeding.

C-reactive protein (CRP) is a plasma protein produced in the liver in response to tissue inflammation [8]. Reportedly, an elevated CRP level may be associated with an increased risk of postoperative complications and poorer overall survival in advanced cancer patients [9]. Although the areas under curve (AUC) were not high, the increase in CRP level significantly correlated with upper gastrointestinal bleeding [9], so an increase in CRP level could also serve as a prognostic indicator for re-bleeding in non-variceal upper gastrointestinal bleeding [11], spontaneous intracerebral hemorrhage [12], and hematoma growth [13].

This study evaluated the independent effect of CRP on the risk of EBB-induced bleeding and

Table 1. Baseline characteristics of the study participants

Characteristics	Biopsy-induced bleeding	
	Yes (n = 218)	No (n = 359)
Age (y), median (range)	66 (36-85)	65 (39-85)
Gender, n (%)		
Male	130 (31.1)	288 (68.9)
Female	37 (29.1)	90 (70.9)
Diabetes, n (%)		
Yes	11 (36.7)	19 (63.3)
No	207 (37.8)	340 (62.2)
Hypertension, n (%)		
Yes	30 (49.2)	31 (50.8)
No	188 (36.4)	328 (63.6)
COPD, n (%)		
Yes	41 (33.3)	82 (66.7)
No	177 (39.0)	277 (61.0)
CHD, n (%)		
Yes	9 (45.0)	11 (55.0)
No	209 (37.5)	348 (62.5)
Location of lesion, n (%)		
Central airway	42 (60.0)	28 (40.0)
Peripheral bronchi	176 (34.7)	331 (65.3)
Histological types, n (%)		
Adenocarcinoma	35 (23.2)	116 (76.8)
Squamous cell carcinoma	134 (45.4)	161 (54.6)
SCLC	36 (37.1)	61 (62.9)
Others	13 (38.2)	21 (61.8)
Stage, n (%)		
Early	90 (31.1)	199 (68.9)
Advanced	128 (44.4)	160 (55.6)
WBC ($\times 10^9$/L)	7.88 ± 0.24	7.23 ± 0.16
Neutrophils ($\times 10^9$/L)	5.98 ± 0.24	5.09 ± 0.15
Neutrophils (%)	72.74 ± 0.76	69.07 ± 1.86
CRP ($mg{\cdot}L^{-1}$)	37.81 ± 3.19	15.56 ± 1.24
Hemoglobin (g/dL)	12.61 ± 0.17	12.78 ± 0.18
Platelets ($\times 10^9$/L)	239.67 ± 6.92	231.03 ± 4.62
PT (S)	14.32 ± 0.86	14.81 ± 0.68
APTT (S)	35.32 ± 1.17	38.22 ± 1.40
ALT ($IU{\cdot}L^{-1}$)	21.42 ± 1.35	21.07 ± 0.77
AST ($IU{\cdot}L^{-1}$)	26.77 ± 1.20	26.08 ± 0.72

COPD, Chronic obstructive pulmonary disease; CHD, coronary heart disease; SCLC, small-cell lung carcinoma; WBC, white blood cell; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

further explored the predictive value of CRP for EBB-induced bleeding in patients with lung cancer. We hypothesized that a higher CRP level is associated with a higher incidence of EBB-induced bleeding events and that the preoperative serum CRP level is a useful prognostic indicator for EBB-induced bleeding.

Materials and methods

Study design

This was a retrospective study using data collected from consecutive patients who had undergone EBB and were diagnosed with lung cancer at the Jinhua Municipal Central Hospital between January 2014 and February 2018. The hospital ethics committee approved this study. The data were anonymous, so the requirement for informed consent was waived.

The following variables were collected: age, sex, comorbidities (chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), hypertension and diabetes), location of the lesions, histological types, stage of cancer (early or advanced), biopsy bleeding results (yes or no), and hemostasis maneuvers. CRP and other blood tests (white blood cell (WBC) counts, neutrophil counts, neutrophils percentage, hemoglobin, platelets, prothrombin time, activated partial thromboplastin time, alanine aminotransferase, and aspartate aminotransferase) were performed on admission or at the first visit, three days prior to the bronchoscopy.

The patients selected met the following inclusion criteria: a. adult patients with endobronchial lesions who underwent forceps biopsies, and b. patients diagnosed with a primary lung cancer. Patients who presented with "proposed risk factors", including thrombocytopenia (platelets < 50 × 10^3/μl), continuous anti-coagulant or anti-platelet therapy, immunosuppression, severe liver and kidney disease, heart function failure, mechanical ventilation, pulmonary arterial hypertension, lung transplant, bleeding tendencies, and active bleeding, were excluded from the study.

A total of 577 patients met the study inclusion criteria. The patients were classified into two

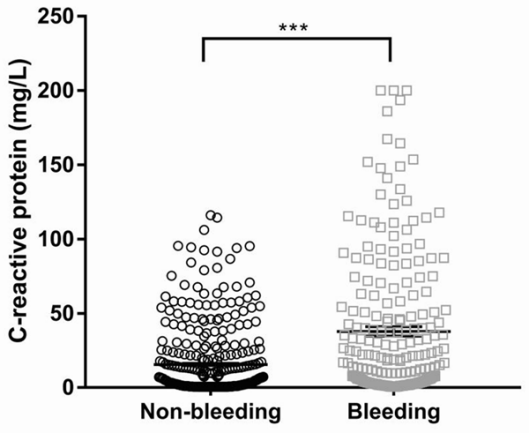

Figure 1. Comparison of C-reactive protein levels between the non-bleeding and the bleeding groups among patients with lung cancer who underwent EBB. The mean C-reactive protein level was significantly higher in the bleeding group compared to the level in the non-bleeding group. ***$P < 0.001$. EBB = endobronchial biopsy.

groups: those who had been treated with hemostasis maneuvers during EBB were classified as the bleeding group (n = 218), and those who did not require hemostasis maneuvers or who did not experience hemorrhage were classified as the non-bleeding group (n = 359). We categorized the patients into early and advanced stages based on their TNM stage (stage I and II as an early stage, and stage III and IV as an advanced stage). In this study, central airways referred to the trachea, left main bronchi, right main bronchi, and right middle bronchus. Peripheral bronchi included the left and right lobar bronchi.

EBB procedures

The procedures were performed under general anesthesia. Propofol (1.0 mg/kg for induction, and 3.0-6.0 mg/kg/h for maintenance) and remifentanil (5.0-10.0 μg/kg/h) were used for sedation and analgesia in general anesthesia, respectively. Cisatracurium, if needed, was used for the induction of neuromuscular blockade. The patients were intubated with a laryngeal mask airway (LMA) (Well Lead Medical Co., Ltd., Guangzhou, China), and ventilated using a closed circuit connected to the ventilator. The bronchoscopic procedures were performedvia LMA. The procedures were performed by two experienced bronchoscopists using a fiberoptic bronchoscope (BF-1T60, Olympus Corp., Tokyo, Japan).

Forceps biopsies were used during the bronchoscopy. Generally, 3-5 biopsies were performed in each patient at the same lesion [3], but only one biopsy was performed when a patient bled significantly following the first biopsy. Diluted adrenalin and/or 4°C physiological saline, and argon plasma coagulation (APC) were used for hemostasis.

Statistical analyses

Descriptive statistics were used to summarize the patients' baseline characteristics. Blood test values are presented as the mean ± standard error of mean, age is indicated as the median (range), and the categorical variables are expressed as the number and percentage. Data are also expressed as the odds ratio (OR) and 95% confidence interval (CI). Between-group comparisons were executed using unpaired *t*-tests, Pearson chi-squared tests or the Fisher's exact, as appropriate. The AUC was used as a measure of diagnostic efficacy. Multivariate regression was conducted for analyzing the independent relationship between CRP levels and biopsy bleeding risk. All analyses were performed using R (The R Foundation; https://www.r-project.org) software. $P < 0.05$ was considered statistically significant.

Results

Of 577 consecutively collected patients, 218 (37.8%) hemorrhaged following EBB, and they received hemostasis maneuvers post-EBB. No case of severe hemorrhage was recorded. The Patients' demographics, clinical characteristics, and blood tests are presented in **Table 1**.

The CRP level was significantly higher in the bleeding group than in the non-bleeding group (**Figure 1**, $P < 0.001$). In addition, the location of the lesion, histological types, stage, sex, WBC, and neutrophil counts positively correlated with EBB-induced bleeding as assessed by univariate analysis (**Table 2**). On adjusting for these characteristics (**Table 3**, adjust I), or on the combined adjustment of risk factors judged by clinical significance (age, diabetes, hypertension, COPD, CHD, and platelets) (**Table 3**, adjust II), the ORs (95% CI) of Q2, Q3, and Q4 of CRP were statistically significant compared with that of Q1 (3.003 (1.660, 5.431), 2.952 (1.618, 5.386), 5.978 (3.245, 11.014) in adjust I model, and 3.213 (1.760, 5.865), 3.069

Table 2. Univariate analysis of possible influencing factors of the risk of biopsy-induced bleeding

Variables	Biopsy-induced Bleeding	
	OR (95% CI)	*P* value
Age (y)	1.02 (1.00, 1.04)	0.1326
Sex		
Female	Reference	
Male	1.64 (1.07, 2.51)	0.0236
Diabetes		
No	Reference	
Yes	0.95 (0.44, 2.04)	0.8971
Hypertension		
No	Reference	
Yes	1.69 (0.99, 2.88)	0.0541
COPD		
No	Reference	
Yes	0.78 (0.51, 1.19)	0.2520
CHD		
No	Reference	
Yes	1.36 (0.56, 3.34)	0.4995
Location of lesion		
Peripheral bronchi	Reference	
Central airway	2.82 (1.69, 4.71)	0.0001
Histological types		
Adenocarcinoma	Reference	
Squamous cell carcinoma	2.76 (1.77, 4.29)	< 0.0001
SCLC	1.96 (1.12, 3.42)	0.0187
Others	2.05 (0.93, 4.51)	0.0739
Stage		
Early	Reference	
Advanced	1.77 (1.26, 2.49)	0.0010
WBC ($\times 10^9$/L)	1.06 (1.01, 1.12)	0.0234
Neutrophils ($\times 10^9$/L)	1.10 (1.04, 1.16)	0.0015
Neutrophils (%)	1.01 (1.00, 1.02)	0.2606
CRP ($mg{\cdot}L^{-1}$)	1.02 (1.01, 1.02)	< 0.0001
Hemoglobin (g/dL)	1.00 (0.99, 1.00)	0.5391
Platelets ($\times 10^9$/L)	1.00 (1.00, 1.00)	0.2819
PT (S)	1.00 (0.98, 1.01)	0.6610
APTT (S)	0.99 (0.98, 1.00)	0.1832
ALT ($IU{\cdot}L^{-1}$)	1.00 (0.99, 1.01)	0.8047
AST ($IU{\cdot}L^{-1}$)	1.00 (0.99, 1.01)	0.5997

COPD, Chronic obstructive pulmonary disease; CHD, coronary heart disease; SCLC, small-cell lung carcinoma; WBC, white blood cell; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(1.657, 5.686), 6.434 (3.402, 12.168) in adjust II model). There was a trend of an increased incidence of EBB-induced bleeding in patients with an elevated CRP level (**Table 3**, P for trend < 0.0001).

We analyzed the predictive role of the preoperative serum CRP level for EBB-induced bleeding (**Figure 2**). With a cutoff value of 1.15 mg/L, serum CRP had a sensitivity of 94.04%, a specificity of 31.20%, a positive predictive value of 45.35%, and a negative predictive value of 89.60%. The AUC for CRP in the bleeding group was 0.692 (95% CI, 0.657-0.739).

Discussion

The present study demonstrated that preoperative elevated serum CRP level is an independent risk factor for bleeding during EBB in patients with lung cancer. Furthermore, our results showed that serum CRP may serve as a useful indicator for predicting the risk of EBB-induced bleeding.

Reportedly, malignant lesions are more likely to bleed upon biopsies than benign mucosal lesions [14]. In some malignant cases, massive blood loss following EBB may occur [15]. A number of risk factors have been proposed for bleeding during bronchoscopy, including immunosuppression, mechanical ventilation, thrombocytopenia (platelets < 50×10^3/μl), anti-coagulant and anti-platelet use, pulmonary arterial hypertension, lung transplant, severe liver and kidney disease, bleeding tendencies and active bleeding [4-7]. However, there is still confl icting evidence regarding some of these proposed risk factors for hemorrhage associated with bronchoscopy [16, 17]. In contrast, most patients who receive EBB do not have the aforementioned risk factors in clinical practice. To the best of our knowledge, currently, there is no effective predictor to evaluate and predict the risk of biopsy bleeding in clinical practice.

CRP, generally acting as a nonspecific infl ammatory marker, has demonstrated its predictive value for bleeding recently in several studies. Tomizawa et al. [10] reported that an elevated CRP level may be indicative of a higher risk of upper gastrointestinal bleeding. With a period of 3-6 months before endoscopy, a more than twofold increase in the serum CRP level indicated bleeding from the

Table 3. Multivariate regression analysis of quartiles of CRP with the risk of biopsy-induced bleeding

Parameter	Biopsy-induced bleeding OR (95% CI) *p*-value		
	Non-adjust	Adjust I[a]	Adjust II[b]
CRP ($mg{\cdot}L^{-1}$)			
Q1 (n = 142) (≤ 1.46)	Reference	Reference	Reference
Q2 (n = 146) (1.47-6.70)	3.585 (2.026, 6.345) < 0.0001	3.003 (1.660, 5.431) 0.0003	3.213 (1.760, 5.865) 0.0001
Q3 (n = 144) (6.71-31.90)	3.775 (2.132, 6.683) < 0.0001	2.952 (1.618, 5.386) 0.0004	3.069 (1.657, 5.686) 0.0004
Q4 (n = 145) (≥ 32.00)	7.934 (4.493, 14.012) < 0.0001	5.978 (3.245, 11.014) < 0.0001	6.434 (3.402, 12.168) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001

CRP, C-reactive protein; COPD, Chronic obstructive pulmonary disease; CHD, coronary heart disease; WBC, white blood cell. [a]Adjust I adjust for: sex, location of lesion, histological types, stage, WBC, and neutrophils. [b]Adjust II adjust for: sex, age, location of lesion, histological types, stage, Diabetes, Hypertension, COPD, CHD, WBC, neutrophil counts, and platelets.

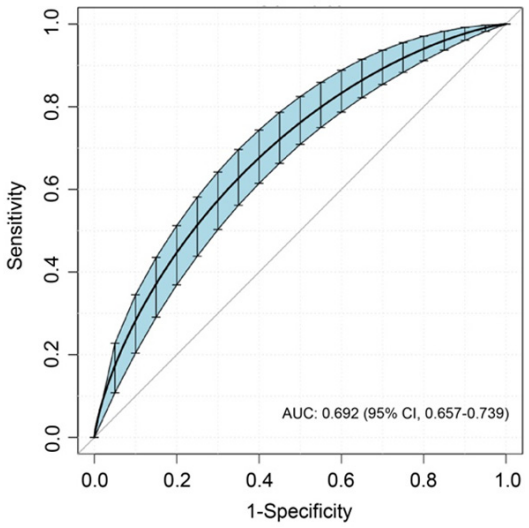

Figure 2. Receiver-operating characteristic curve analysis of the C-reactive protein levels to predict EBB-induced bleeding in patients with lung cancer. The AUC indicates the diagnostic power of the C-reactive protein level (Bootstrap resampling times = 500). EBB = endobronchial biopsy; AUC = area under the curve; CI = confidence interval.

upper gastrointestinal tract [10]. Furthermore, in a retrospective study including 453 patients, Lee et al. [11] noted that CRP could serve as a useful prognostic indicator for re-bleeding in nonvariceal upper gastrointestinal bleeding. Elhechmi et al. [12], in a retrospective analysis, demonstrated that H24-CRP may be a more reliable marker than initial CRP in the prediction of mortality by intracerebral hemorrhage. Another study showed that CRP > 10 mg/L was independently predictive of early hematoma growth in patients with primary or vitamin K antagonist-associated spontaneous intracerebral hemorrhage [13].

In our study, we found that a preoperative elevated serum CRP level was associated with an increased incidence of EBB-induced bleeding. After adjustment for the main confounding risk factors (sex, location of the lesion, histological types, stage, WBC, and neutrophil counts) and factors considered to be clinically relevant (age, diabetes, hypertension, COPD, CHD, and platelets), the strength of this association did not change. The predictive role of serum CRP for EBB-induced bleeding was further analyzed. Although the AUC (0.692; 95% CI, 0.657-0.739) was not high, with a cutoff value of 1.15 mg/L, CRP showed a relatively high sensitivity (94.04%) and negative predictive value (89.60%), which may help physicians guide patient selection for bronchoscopy and bleeding management during EBB. Moreover, the serum CRP test is widely available and inexpensive in clinical practice, suggesting that it is feasible and a useful indicator for predicting bronchoscopic, biopsy-induced hemorrhage.

The strengths of the present study included the inclusion of consecutive patients, having experienced bronchoscopists, using only one biopsy method (endobronchial forceps biopsy), and a relatively fixed number of biopsies, as well as a relatively fixed CRP detection time before bronchoscopy. However, some limitations of the current study should be acknowledged. First, it was difficult to accurately measure blood loss during bronchoscopy [18]. A quantitative measurement of blood loss follow-

ing EBB could not be provided in our study. We divided participants into a bleeding group and a non-bleeding group based just on whether they received hemostasis post-EBB, which may lead to inaccurate grouping in some patients with minimal bleeding. Second, as serum CRP level is a nonspecific infl ammatory marker, its concentration may change over time. In addition, CRP is susceptible to the clinical context of the patient. Although we adjusted for the main confounding factors, this study was inevitably subject to the potential limitations of the use of observational data. Further validation in prospective studies is warranted.

Conclusions

The current study showed that preoperative elevated serum CRP level was an independent risk factor for EBB-induced bleeding in the lung cancer population, suggesting that preoperatively reducing CRP levels may improve intraoperative biopsy bleeding and thus help guide the timing of biopsies. Moreover, preoperative serum CRP has the potential to be a useful prognostic indicator for EBB-induced bleeding, which may be a valuable reference for the selection of biopsy patients and the management of EBB-induced bleeding.

Acknowledgements

This study was supported by the Medical and Health Science and Technology Plan Project of Zhejiang Province (no. 2018RC079), the Youth Research Fund of Jinhua Hospital of Zhejiang University (no. JY2017205) and Zhejiang Province Bureau of Health (no. 2014KYB295).

Disclosure of conflict of interest

None.

Address correspondence to: Shun-Jin Zhao, Department of Respiratory Medicine, Lanxi People's Hospital, No. 1359, Xishan Road, Lanxi 321100, Zhejiang Province, China. Tel: +86 579 88669881; Fax: +86 579 88669882; E-mail: 20969971@qq.com

References

[1] Herth FJF. Bronchoscopy and bleeding risk. Eur Respir Rev 2017; 26.

[2] Chinsky K. Bleeding risk and bronchoscopy: in search of the evidence in evidence-based medicine. Chest 2005; 127: 1875-7.

[3] Rivera MP, Detterbeck F, Mehta AC; American College of Chest Physicians. Diagnosis of lung cancer: the guidelines. Chest 2003; 123: 129S-136S.

[4] Brickey DA, Lawlor DP. Transbronchial biopsy in the presence of profound elevation of the international normalized ratio. Chest 1999; 115: 1667-1671.

[5] Herth FJ, Becker HD, Ern A. Aspirin does not increase bleeding complications after transbronchial biopsy. Chest 2002; 122: 1461-1464.

[6] Diette GB, Wiener CM, White P Jr. The higher risk of bleeding in lung transplant recipients from bronchoscopy is independent of traditional bleeding risks: results of a prospective cohort study. Chest 1999; 115: 397-402.

[7] Wang S, Ye Q, Tu J, Song Y. The location, histologic type, and stage of lung cancer are associated with bleeding during endobronchial biopsy. Cancer Manag Res 2018; 10: 1251-1257.

[8] Ansar W, Ghosh S. C-reactive protein and the biology of disease. Immunol Res 2013; 56: 131-42.

[9] Blakely AM, Heffernan DS, McPhillips J, Cioffi WG, Miner TJ. Elevated C-reactive protein as a predictor of patient outcomes following palliative surgery. J Surg Oncol 2014; 110: 651-655.

[10] Tomizawa M, Shinozaki F, Hasegawa R, Togawa A, Shirai Y, Ichiki N, Motoyoshi Y, Sugiyama T, Yamamoto S, Sueishi M. Reduced hemoglobin and increased C-reactive protein are associated with upper gastrointestinal bleeding. World J Gastroenterol 2014; 20: 1311-1317.

[11] Lee HH, Park JM, Lee SW, Kang SH, Lim CH, Cho YK, Lee BI, Lee IS, Kim SW, Choi MG. The serum C-reactive protein was an independent risk factor for 30-day rebleeding in patients with acute nonvariceal upper gastrointestinal bleeding. Dig Liver Dis 2015; 47: 378-383.

[12] Elhechmi YZ, Hassouna M, Chérif MA, Ben Kaddour R, Sedghiani I, Jerbi Z. Prognostic value of serum C-reactive protein in spontaneous intracerebral hemorrhage: when should we take the sample? J Stroke Cerebrovasc Dis 2017; 26: 1007-1012.

[13] Di Napoli M, Parry-Jones AR, Smith CJ, Hopkins SJ, Slevin M, Masotti L, Campi V, Singh P, Papa F, Popa-Wagner A, Tudorica V, Godoy DA. C-reactive protein predicts hematoma growth in intracerebral hemorrhage. Stroke 2014; 45: 59-65.

[14] Ozgül MA, Turna A, Yildiz P, Ertan E, Kahraman S, Yilmaz V. Risk factors and recurrence patterns in 203 patients with hemoptysis. Tuberk Toraks 2006; 54: 243-248.

[15] Jin F, Mu D, Chu D, Fu E, Xie Y, Liu T. Severe complications of bronchoscopy. Respiration 2008; 76: 429-433.

[16] Carr IM, Koegelenberg CF, von Groote-Bidlingmaier F, Mowlana A, Silos K, Haverman T, Dia-

con AH, Bolliger CT. Blood loss during fl exible bronchoscopy: a prospective observational study. Respiration 2012; 84: 312-318.

[17] Zahreddine I, Atassi K, Fuhrman C,Febvre M, Maitre B, Housset B. Impact of prior biological assessment of coagulation on the hemorrhagic risk of fiberoptic bronchoscopy. Rev Mal Respir 2003; 20: 341-346.

[18] Schumann C, Hetzel M, Babiak AJ, Hetzel J, Merk T, Wibmer T, Lepper PM, Krüger S. Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. J Thorac Cardiovasc Surg 2010; 139: 997-1000.