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ORIGINAL RESEARCH

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Non-high risk PE in the patients with acute or exacerbated respiratory disease: the value of the algorithm based on D-dimer evaluation and Revised Geneva Score

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Abstract

Introduction: The diagnostic algorithm of non-high risk pulmonary embolism (PE) is based on probability scoring systems and plasma D-dimer (DD) assessment. The aim of the present study was to investigate the efficacy of Revised Geneva Scoring (RGS) and DD testing for the excluding of non-high risk PE, in the patients admitted to the hospital due to acute respiratory diseases.
Material and methods: The consecutive patients, above 18 years of age, referred to the department of lung diseases, entered the study. The exclusion criteria were: the pregnancy and the suspicion of high risk PE. Plasma DD was measured with quick ELISA test, VIDAS D-dimer New, bioMerieux, France. Multislice computed tomography angiography was performed in all of the patients.
Results: 153 patients, median age 65 (19–88) years entered the study. The probability of PE was: low — in 58 patients (38%), intermediate — in 90 (59%), high — in 5 (3%). DD < 500 ng/ml was found in 12% of patients with low and intermediate probability of PE. PE was recognized in 10 out of 153 patients (7%). None of the patients with DD < 500 ng/ml was diagnosed with PE (NPV 100%). Median DD value was significantly higher in PE patients comparing to non-PE (4500 ng/ml and 1356 ng/ml respectively, $p = 0.006$).
Conclusion: In the group of the patients with acute respiratory symptoms, low or intermediate clinical probability scoring combined with normal DD had a high NPV in excluding PE. Nevertheless, such approach was not very effective, as the increased DD was noted in 88% of the examined population.

Key words: d-dimer, pulmonary embolism, probability assessment, respiratory diseases

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Introduction

Venous thromboembolic disease (VTE) is a common and potentially life threatening disease, with the incidence rate of 100–200/100 000 in Europe and in the United States of America [1, 2]. The risk factors, such as: previous episodes of deep vein thrombosis, immobilization, trauma, neoplastic disease, markedly increase the probability of VTE [3–5]. According to recent publications, incidence of VTE is also increased in the patients with chronic lung disorders, such as: chronic obstructive pulmonary disease (COPD) [6], severe asthma [7], idiopathic pulmonary fibrosis [8] and sarcoidosis [9, 10].

The diagnostic algorithm of non-high risk PE is based on probability scoring systems, such as Wells Score or Revised Geneva Score (RGS) [11]. In the patients with low and intermediate probability

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of PE, plasma D-dimer (DD) evaluation is the next diagnostic step, according to ESC guidelines [11]. The quantitative DD tests based on enzyme-linked immunosorbent assays are recommended for this procedure [11]. Normal D-dimer concentration (< 500 ng/mL) in the patient with low or intermediate probability of PE has high negative predictive value (NPV) for VTE [12]. The risk of PE development in such population is less than 1% in 3 months of subsequent follow up [12].

DD is a non-specific marker indicating the activation of the process of fibrin turnover. Elevated DD concentrations were reported in pregnancy, pneumonia, sepsis, Alzheimer's disease, arterial thrombosis, and malignancy [13–15]. Moreover DD level correlates with age and increases in the patients above 50 years of age [16, 17]. Recently, Schouten et al. proposed the age adjusted DD cut off (age × 10 ng/mL) [18]. The authors of the ADJUST-PE study found that age-adjusted DD threshold is combined with improvement of specificity without loosing of the sensitivity of the model of PE prediction based on clinical probability and DD [19]. Nevertheless, according to Woller et al. further validation is needed to finally approve such diagnostic approach [20]. Renal insufficiency may also influence DD concentration, but the increase of DD in the patients with GRF 30–60 mL/min is moderate [21].

The value of PE diagnostic algorithm based on probability scoring and DD was not investigated extensively in the patients with acute or exacerbated respiratory diseases. Thus the aim of the present study was to investigate the efficacy of RGS and DD testing for the excluding of non-high risk PE, in the patients admitted to the hospital due to acute respiratory symptoms.

Material and methods

The consecutive patients, above 18 years of age, referred in 2013 to the Ist Department of Lung Diseases of the National Institute of Tuberculosis and Lung Diseases in Warsaw due to acute respiratory symptoms, entered the study. The exclusion criteria were: the pregnancy and the suspicion of high risk PE, based on the signs of shock or significant hypotension defined as the decrease of systolic blood pressure to the value below 90 mm Hg or greater than 40 mm Hg, for at least 15 minutes [10].

The PE probability was assessed with RGS (Table 1). Plasma DD was measured in all of the patients, on 1–3 hospital day, with quick ELISA test, VIDAS D-dimer New, bioMerieux, France. Threshold value for DD was 500 ng/mL according to manufacturer's recommendations.

Multislice computed tomography angiography (CTA) was performed in all of the patients with a 16-detector scanner (Siemens Somatom Sensation 16) according to "pulmonary embolism" protocol. 80 mL of low osmotic, iodine contrast medium was used (intravenous injection, with an automatic syringe).

The following clinical and laboratory parameters were recorded: dyspnea, chest pain, hemoptysis, cough, purulent expectoration, increased body temperature on admission (> 38°C), morphological blood analysis, CRP, and blood gas analysis.

Statistical analysis

A database and all analyses were performed using STATISTICA 6.0 (Statsoft) computer software. The results were expressed as median values and ranges. For comparison of categorical variables between the groups — the Fisher test was used, for continuous variables — U Mann-Whitney and Kruskal-Wallis tests were applied. P-value < 0.05 was considered statistically significant.

Results

153 patients (84 males and 69 females), median age 65 (19–88) years entered the study. Clinical characteristics of the study population is presented in Table 2. Most frequent complaints

Table 1. Revised Geneva Scoring

Variables	Points
Predisposing factors	
age > 65 years	1
Previous DVT or PE	3
Surgery of fracture within one month	2
Active malignancy	2
Symptoms	
Unilateral lower limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate	
75 to 94 per minute	3
≥ 95 per minute	5
Pain on lower limb deep vein palpation or unilateral oedema	4
Clinical probability	Low: 0–3 point, intermediate: 4–10 points, High: ≥ 11 points

Table 2. Clinical characteristics of the examined population and comparison of PE and non-PE patients (pts)

Clinical characteristics	Total No 153	PE pts No 10	Non-PE pts No 143	P PE vs. non PE
Age (median, range)	65.0 (19.0–88.0)	65.5 (43.0–81.0)	65.0 (19.0–88.0)	0.85
Gender males/females	84/69 (54.9/45.1%)	7/3 (70/30%)	77/66 (53.8/46.1%)	0.51
Dyspnea n (%)	111 (72.5)	8 (80.0)	103 (72.0)	0.73
Chest pain n (%)	38 (24.8)	5 (50.0)	33 (23.1)	0.12
Cough n (%)	107 (69.9)	6 (60.0)	101 (70.6)	0.49
Hemopthysis n (%)	31 (20.3)	2 (20.0)	29 (20.3)	1.0
Purulent sputum n (%)	24 (15.7)	0 (0.0)	24 (16.8)	0.36
Temp > 38°C	41 (26.8)	2 (20.0)	39 (27.3)	1.0
VTE med. hist. n (%)	15 (9.8)	3 (30.0)	12 (8.4)	0.06
Risk factors n (%)	35 (22.9)	3 (30.0)	32 (22.4)	0.7
Revised Geneva Score (median)	4 (0–11)	4.5 (0–11)	4.0 (0–11)	0.92

PE — pulmonary embolism; VTE — venous thromboembolic disease

were: dyspnea (72%) and cough (69.9%). Hemoptysis and pleuritic chest pain were found in 20% and 24.8% of patients respectively.

RGS revealed low probability of PE — in 58 patients (38%), intermediate probability — in 90 (59%) and high probability — in 5 (3%). DD < 500 ng/mL was found in 18 out of 148 patients with low and intermediate probability of PE (12%): in 3/58 of patients with low probability of PE (5%) and in 15/90 of patients with intermediate probability of PE (16%).

PE based on CTA was recognized in 10 out of 153 patients (7%): 4/58 (7%) of low probability population, 4/90 (4%) of intermediate probability and 2/5 (40%) of high probability. The thrombi were localized in lobar pulmonary arteries — (2 patients), in segmental pulmonary arteries — (3 patients), both lobar and segmental — pulmonary arteries — (4 patients), sub-segmental arteries (1 patient). Radiological signs of lung infarcts and/or pleural fluid were found in 2 patients. In 7 out of 10 PE patients other pathology was additionally diagnosed: lung cancer — in 2 patients, pneumonia, COPD, sarcoidosis, idiopathic lung fibrosis and heart insufficiency — in 1 patient each.

The final diagnosis in those patients in whom PE was excluded was: neoplastic disease of the chest (lung cancer, thymoma, mesothelioma) — in 45 patients (pts), community acquired pneumonia (CAP) — in 18 pts, exacerbation of asthma or COPD — in 15 pts, idiopathic pulmonary fibrosis (IPF) — in 10 pts, other interstitial lung disease — in 19 pts, infective exacerbation of cystic fibrosis (CF) or non-CF bronchiectasis — in 11 pts, organizing pneumonia (OP) or bronchiolitis obliterans (BO) — in 7 pts, heart failure — 3 pts, vasculitis — 4 pts, tuberculosis or non-tuberculous mycobacterial lung disease (NTMLD) — 3 pts, other lung diseases — 8 pts.

The comparison of clinical characteristics of the group with PE and of the remaining patients (Table 2) revealed that VTE history was more frequent in the patients with PE comparing to non-PE (30% vs. 8.4%, p = 0.06). Purulent expectoration hasn't been noted in PE, but it was also rarely recorded in the remaining patients (16.8%). Chest pain was more frequent in PE than in non-PE patients (50% vs. 23.1%), nevertheless the difference was not significant. Dyspnea, hemoptysis and increased body temperature were reported with the same frequency in PE and non-PE patients.

DD < 500 ng/mL was found in 18/153 patients (12%). None of the patients with DD < 500 ng/mL was diagnosed with PE. The results of the diagnostic algorithm based on RGS, DD and CTA are shown on Figure 1. The diagnostic value of DD < 500 ng/mL for the exclusion of PE in low/intermediate risk patients was high: sensitivity — 100%, negative predictive value — 100%.

Median DD value in PE patients was 4500 (525.0–5860.0) ng/mL and it was significantly higher than in the remaining patients, in whom median DD was 1356 (105.0–33935.0) ng/mL, p = 0.006. Elevated plasma DD was found in 135/153 (88%) patients: in 10 patients it was observed in the course of PE episode, in the remaining patients — in the course of other lung pathologies listed in Table 3.

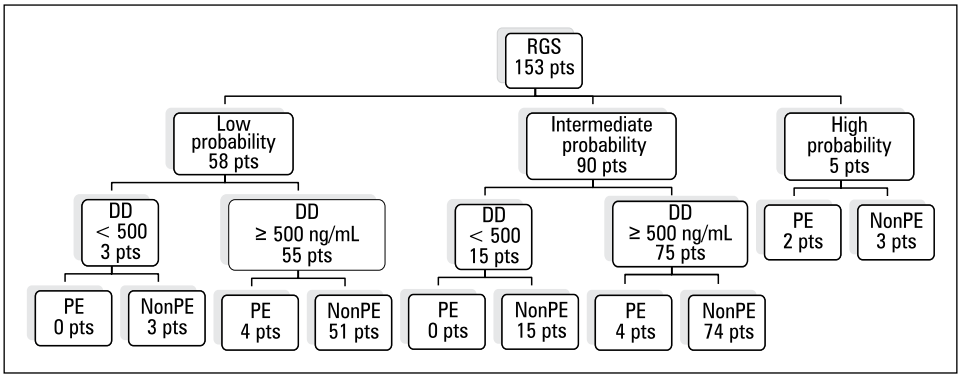

Figure 1. PE recognition based on Revised Geneva Scoring, D-dimer assessment and computed tomography angiography

Table 3. D-dimer (DD) concentration according to clinical diagnosis

Diagnosis	No of pts	Median DD [ng/ml]	Range [ng/ml]	> 500 No(%) [ng/ml]	P vs. PE
Neoplastic disease	45	1741.0	292.0–28144.0	41 (91)	0.03
Pneumonia + tuberculosis, NTMLD	21	1870.0	179.0–9266.0	19 (90)	NS
COPD/astma	15	861.1	258–2825.24	11 (73)	0.001
IPF	10	780.45	257.58–1833.0	7 (70)	0.003
Other ILD	19	1089.0	268.0–5409.4	18 (95)	0.02
OP/BO	7	2194.0	1106.0–13201.0	7 (100)	NS
CF, bronchiectasis	11	1177.0	169.0–33935.0	10 (91)	0.02
Hemopthysis, heart failure, others	11	723.0	105.0–4361.0	9 (82)	0.006
Vasculitis	4	3129.41	266.0–6467.0	3 (75)	NS
PE	10	4500.0	525.0–5860.0	10 (100)	
Total	**153**	**1466.0**	**105.0–33935.0**	**135 (88)**	

NTMLD — nontuberculous mycobacterial lung disease; IPF — idiopathic pulmonary fibrosis; ILD — interstitial lung disease; OP — organizing pneumonia; BO — bronchiolitis obliterans; PE — pulmonary embolism; NS — non-significant

The highest median DD values in non-PE patients were observed in the course of vasculitis (3129.4 ng/mL), OP/BO (2194 ng/mL), CAP (1870 ng/mL), neoplastic disease (1741 ng/mL), infective exacerbation of CF or bronchiectasis (1177 ng/mL), the lowest — in COPD/astma exacerbation and in IPF (Table 3, Figure 2). The statistical significance of the obtained results of DD in various lung diseases comparing to PE patients are presented in Table 3.

The comparison of the remaining laboratory parameters between the PE patients and groups with other lung diseases (Table 4) revealed that CRP value was significantly higher in CAP than in PE patients, median values were 135.4 ng/mL and 34.46 ng/mL respectively ($p < 0.03$) (Figure 3).

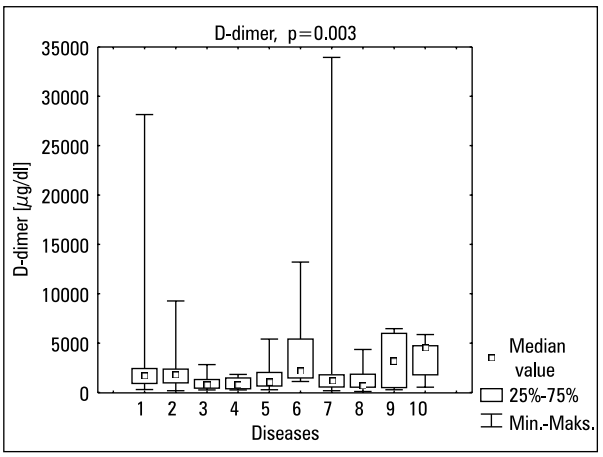

Figure 2. DD-values according to clinical diagnosis

Diseases: 1 — neoplastic disease; 2 — pneumonia, tuberculosis, nontuberculous mycobacterial lung disease; 3 — COPD, astma; 4 — idiopathic pulmonary fibrosis; 5 — other interstitial lung diseases; 6 — organizing pneumonia, bronchiolitis obliterans; 7 — cystic fibrosis, bronchiectasis; 8 — hemoptysis, heart failure, others; 9 — vasculitis; 10 — pulmonary embolism. P-values in Table 3

Discussion

In the present study, PE based on CTA was recognized in 10 out of 153 patients (7%) with

Table 4. Other laboratory parameters according to clinical diagnosis (median, range)

Diagnosis	No of pts	WBC	Neutr.	HGB	PLT	CRP	pO_2	pCO_2
Neoplastic disease	45	7.79 (2.81–37.37)	5.8 (0.95–31.71)	13.2 (8.0–16.0)	276 (104–594)	31 (4.0–204.1)	66.45 (44.8–88.0)	34.05 (18.7–59.1)
Pneumonia (+ tuberculosis, NTMLD)	21	9.8 (3.3–28.9)	7.44 (1.42–25.3)	12.4 (8.6–15.3)	335.0 (100.0–560.0)	135.4 (4.0–366.0)	62.7 (48.6–94.0)	33.9 (22.8–50.4)
COPD/astma	15	9.42 (3.9–16.15)	6.35 (1.98–13.8)	13.9 (8.8–16.0)	278.0 (71.0–583.0)	11.4 (4.0–141.0)	60.9 (49.9–89.0)	37.6 (27.7–49.4)
IPF	10	9.21 (5.48–17.64)	6.06 (3.39–16.51)	15.1 (12.3–16.6)	248.5 (121.0–287.0)	8.6 (4.0–60.4)	63.35 (41.6–76.5)	35.25 (29.0–42.0)
Other ILD	19	7.8 (4.49–17.9)	5.26 (0.61–14.1)	13.7 (8.6–17.8)	267 (159.0–604.0)	12.5 (4.0–53.0)	66.9 (44.0–97.8)	34.3 (25.9–45.9)
OP/BO	7	9.73 (7.09–10.9)	6.93 (4.34–8.77)	12.4 (12.0–14.41)	332.0 (250.0–617.0)	12.5 (7.8–215.5)	62.7 (49.8–74.0)	32.5 (22.2–41.4)
CF, bronchiectasis	11	9.96 (4.92–18.02)	7.48 (2.67–15.14)	11.9 (11.1–14.6)	277.0 (78.0–528.0)	27.8 (4.0–165.2)	68.0 (52.7–101.9)	36.1 (32.2–58.6)
Hemopthysis, heart failure, others	11	7.36 (4.03–11.0)	4.23 (2.29–5.94)	14.2 (10.5–15.18)	249.0 (116.0–352.0)	6.6 (4.0–26.6)	72.0 (54.5–93.0)	36.0 (27.0–39.9)
Vasculitis	4	10.86 (5.99–13.69)	6.99 (3.39–11.65)	11.6 (10.2–12.7)	347.5 (68.9–377.0)	86.1 (7.8–169.0)	68.7 (58.9–86.6)	34.15 (30.5–37.2)
PE	10	10.99 (6.9–15.79)	7.78 (1.59–10.52)	13.9 (9.2–15.6)	283.5 (147.0–834.0)	34.4 (4.0–198.9)	66.6 (45.9–87.3)	34.05 (28.5–46.0)
Total	153	8.78 (2.81–37.37)	5.81 (0.61–31.78)	13.2 (8.0–17.8)	280.0 (68.9–834.0)	19.8 (4.0–366.0)	65.95 (41.6–101.9)	34.55 (18.7–59.1)
P*		0.19	0.11	0.001	0.058	< 0.00001	0.42	0.66

NTMLD — nontuberculous mycobacterial lung disease; IPF — idiopathic pulmonary fibrosis; ILD — interstitial lung disease; OP — organizing pneumonia; BO — bronchiolitis obliterans; PE — pulmonary embolism

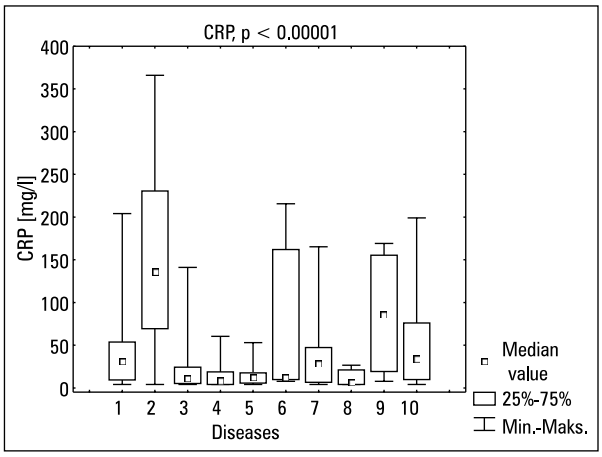

Figure 3. CRP values according to clinical diagnosis

Diseases: 1 — neoplastic disease; 2 — pneumonia, tuberculosis, nontuberculous mycobacterial lung disease; 3 — COPD, astma; 4 — idiopathic pulmonary fibrosis; 5 — other interstitial lung diseases; 6 — organizing pneumonia, bronchiolitis obliterans; 7 — cystic fibrosis, bronchiectasis; 8 — hemoptysis, heart failure, others; 9 — vasculitis; 10 — pulmonary embolism. P-value: 10 vs. 2 p = 0.03; 10 vs. 8 p = 0.03

acute respiratory symptoms: 7% of low PE probability population, 4% of intermediate probability and 40% of high probability. The frequency of PE in our material was slightly lower than reported in meta -analysis of Ceriani et al., who found PE confirmed on CTA in 9% of low probability patients, 26% — of intermediate probability and 76% of high probability ones [22]. This difference could be possibly related to the patients characteristics. The population evaluated by RGS in Ceriani's study was composed of the outpatients and our population consisted of patients hospitalized due to acute lung disease.

In our population, the algorithm of VTE probability assessment based on RGS and DD, had a high NPV (100%), as none of the patients with DD < 500 ng/mL and low or intermediate probability of PE, was diagnosed with PE. Nevertheless, low DD was found only in 12% of patients with acute lung disease, therefore its clinical utility in this population was low. The same problem was noted by Fijałkowska et al., who analyzed 619 patients with both acute and chronic lung pathology and found DD elevation in 63% of patients [23]. Kline et al. found positive DD in 84% of patients hospitalized on medical and emergency wards with the suspicion of PE, and confirmed PE in 19% of patients only [24]. The increase of DD cut off value from 500 ng/mL to 1000 ng/mL, in the patients with RGS lower than 6 points, resulted in the improvement of diagnostic utility of such algorithm, nevertheless it was combined with the slightly increased risk of missing isolated sub-segmental PE [24]. In our group of patients the increase of DD threshold from 500 ng/mL to 1000 ng/mL would result in missing one PE case in the patient with intermediate probability of PE.

In the present study, median DD in PE patients was 4500 ng/mL and it was significantly higher than in non-PE group. The same observation was made by Lippi et al. who found DD > 3000 ng/mL indicative of VTE in the population of large urban emergency department [25].

The highest median DD values in non-PE lung diseases were observed by us in the course of vasculitis (3129.4 ng/mL), and in OP/BO (2194 ng/mL). Nevertheless it is difficult to comment on this issue, as vasculitis was recognized in 4 patients only and OP/BO — in 7 patients. According to our best knowledge no other data concerning this subject has been published.

The frequent cause of DD elevation in the present study was the community acquired pneumonia. Median DD concentration in CAP patients was 1870 ng/mL, the difference between CAP and PE concerning DD value, was not significant. Milbrandt et al. assessed DD concentration (latex immunoassay, cut off value 256 ng/mL) in 934 patients hospitalized due to CAP and found DD elevation in 80.6% of them [26]. Moreover, no substantial changes of DD have been observed during the first 7 days of CAP treatment [26]. The authors suggested that local activation of coagulation, mediated by tissue factor (TF), was the cause of increased DD concentration in pneumonia. The TF, expressed on alveolar macrophages, neutrophils and endothelial cells, might be responsible for systemic coagulopathy during lung infection. The authors found that DD elevation was a negative prognostic factor in CAP: DD 256–1000 ng/mL was combined with 2–3 fold higher mortality rate and DD > 1000 ng/mL — with 5 fold higher mortality rate [26]. Snijders et al. and Agapakis et al. found DD concentration significantly higher in patients with severe CAP (CURB-65 score 3–5) comparing to the others [27, 28].

The other frequent cause of DD elevation in our study was neoplastic disease of the chest (lung cancer, thymoma, mesothelioma). Median DD was 1741 ng/mL, the values were significantly lower than in PE patients. Fijałkowska et al. found DD increase in the course of lung cancer in 75% of patients, with median value of 941 ng/mL [23]. The histological type of neoplasm and the disease extension are probably influencing DD-concentration [23, 29].

Relatively lower DD values were found by us in the course of asthma or COPD exacerbation.

According to Sabit et al. hypoxia and systemic inflammation are responsible for pro-coaguable status in COPD, manifesting mainly as the increase of thrombin-antithrombin complex, but not DD concentration [30]. Accordingly, Silva et al. found no difference in DD concentration between stable COPD patients and the control subjects [31]. The increase of DD concentration in COPD may be caused by infective exacerbation. Nevertheless, data from literature indicate that VTE has been responsible for DD increase in 5–38% of patients with COPD exacerbation [32, 33]. Choi et al. found that DD ≥ 500 ng/mL and the absence of symptoms of respiratory infection, were the significant predictors of PE in the Korean patients with COPD exacerbation [32]. Fruchter et al. found that elevated DD was a reliable prognostic marker for those COPD patients in whom PE was excluded [34].

In our study, median DD in the patients diagnosed with interstitial lung disease was 780.45 ng/mL (IPF) and 1089 ng/mL (non-IPF), and they were significantly lower than in PE patients. There is not much data in literature concerning DD assessment in the patients with ILDs. Bargagli et al. found significantly increased DD in IPF comparing to the controls [35].

Increased DD in the course of ILDs exacerbation may suggest the PE occurrence. Luo et al. found PE in 26% of the patients with exacerbation of ILDs, the factors increasing the probability of PE were: dyspnea, palpitations, lower extremity edema, and positive D-dimer [36].

As in majority of the patients in our study PE could not be excluded based on RGS and DD, we tried to find whether the other clinical and/or laboratory parameters would be helpful in predicting or excluding PE. The analysis of clinical parameters revealed that previous history of VTE was more frequent in PE patients. The remaining clinical features such as dyspnea and hemoptysis were not helpful in differential diagnosis. Pleuritic chest pain was more frequent in PE patients comparing to the others, but this difference was not significant.

The analysis of laboratory parameters revealed that CRP value was significantly higher in CAP comparing to PE. In contrast to general population, hypoxemia and hypocapnia, were not indicative for PE in the examined group of patients with acute respiratory symptoms.

Conclusion

In the examined group of the patients with acute or exacerbated lung diseases low or intermediate clinical probability scoring combined with normal DD (< 500 ng/mL) had a high NPV in excluding PE. Nevertheless, such approach was not very effective, as the increased DD (> 500 ng/mL) was noted in 88% of the examined population. Although median DD was the highest in PE patients, relatively high DD were found also in the course of vasculitis, OP/BO, CAP and neoplastic disease. The probability of PE was higher in the patients with previous history of VTE. High CRP was indicative of CAP.

Conflict of interest

The authors declare no conflict of interest.

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