Prevalence and Predictors of Pulmonary Embolism in Korean Patients with Exacerbation of Chronic Obstructive Pulmonary Disease

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Key Words

Chronic obstructive pulmonary disease • Exacerbation • Prevalence • Pulmonary embolism • Risk factors

Abstract

Background: Data concerning the rate of pulmonary embolism (PE) in Asian patients with chronic obstructive pulmonary disease (COPD) exacerbation are sparse, and no study has shown predictors of PE in these patients. **Objectives:** The purpose of the present study was to investigate the prevalence and predictors of PE in Korean patients with COPD exacerbation. **Methods:** Hospitalized patients with COPD exacerbations were prospectively enrolled into this study and underwent computed tomography (CT) pulmonary angiography and indirect CT venography. **Results:** The most common cause of COPD exacerbation was lower respiratory tract infection (82%; n = 84), followed by PE (5%; n = 5). Eight patients (8%) had venous thromboembolism, and deep vein thrombosis (DVT) was seen in 6%, with proximal DVT in 4%. On multivariate analysis, the absence of symptoms of respiratory infection and plasma D-dimer elevation ($\geq 500 \mu\text{g/l}$) were significant factors predicting PE in patients with COPD exacerbations (odds ratio 31, 95% confidence interval 2–563, $p = 0.02$, and odds ratio 25, 95% confidence interval 1–464, $p = 0.03$, respectively). **Conclusions:** PE comprises approxi-

mately 5% of the etiologies of COPD exacerbations in Koreans. The absence of symptoms suggestive of respiratory infection and elevated plasma D-dimer levels were significant predictors of PE in this population.

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Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with morbidity and mortality [1]. At present, COPD exacerbation is defined mainly based on its symptoms, in terms of either clinical presentation or utilization of health care resources [2]. Consequently, the definition of COPD exacerbation is nonspecific, and this condition can result from a variety of causes. With regard to the importance of COPD phenotypes [3, 4], attempts to phenotype COPD exacerbations have been made, since the clinical spectrum of COPD exacerbation is heterogeneous [2]. The most common causes of exacerbation are infection of the tracheobronchial tree and air pollution, but in up to 30% of exacerbations, the specific cause cannot be identified [5].

Recently, there have been a few prospective studies [6–8] directly targeting the prevalence of pulmonary embolism (PE) in COPD exacerbations. Its prevalence has been

found to range from 3–14% in studies [7, 8] including cases caused by respiratory infection to 25% for only patients with COPD exacerbations of unknown origin [6]. Since PE can lead to cough and dyspnea, similarly to infectious events [9], there is a difficulty in excluding lower respiratory tract infection. Thus, we believe that studies including patients with suspected respiratory infection may lead to results closer to real-world clinical practice than those including only patients with unknown etiology. Generally, the prevalence of venous thromboembolism (VTE) including PE has been found to be markedly lower in Asians than in whites and African Americans [10–12]. However, no study concerning the rate of PE in Asian patients with COPD exacerbation has been published. To the best of our knowledge, no study has yet identified the factors predicting whether PE may lead to COPD exacerbation.

The purpose of this study was to investigate the prevalence of PE and deep vein thrombosis (DVT) in Koreans with COPD exacerbation and to examine predictors of PE as one of the causes of COPD exacerbation.

Materials and Methods

Study Population

Between August 2008 and July 2011, all consecutive patients hospitalized at the Kyungpook National University Hospital, a tertiary referral center in Daegu, South Korea, and diagnosed with COPD exacerbation were prospectively enrolled into this study. The study protocol was approved by the Institutional Review Board of the Kyungpook National University Hospital, and informed consent was obtained from all participants. According to the criteria of the Global Initiative for Chronic Obstructive Lung Disease [4], the diagnosis of COPD was made based on available spirometric data and medical records. COPD exacerbation was defined as acute deterioration from a stable condition, which required hospitalization [6]. On arrival at the hospital, emergency or internal medicine department physicians evaluated the patients by means of history taking, physical examination, chest radiographs and routine laboratory tests. Patients with any specific causes identified on these examinations, including pneumonia, pneumothorax and congestive heart failure, were excluded. After exclusion, all remaining patients underwent computed tomography (CT) pulmonary angiography and indirect CT venography within 24 h of admission to the hospital. Patients with azotemia (serum creatinine >1.5 mg/dl), a hypersensitivity reaction to contrast media, under anticoagulation therapy for any causes or undergoing mechanical or noninvasive positive pressure ventilation were excluded. The etiology of COPD exacerbations was determined as follows: (1) pneumonia was diagnosed when consolidation or ground-glass opacity (GGO) was seen on CT scan with or without symptoms of respiratory infection, including increased sputum, purulent sputum, fever or upper respiratory infection symptoms (sore throat or rhinorrhea with myalgia); (2) tracheo-

bronchitis was diagnosed if symptoms suggestive of respiratory infection were identified without consolidation or GGO on CT scan or if centrilobular nodules or a tree-in-bud pattern was seen on CT imaging, without consolidation or GGO, regardless of these symptoms; (3) congestive heart failure was diagnosed when CT findings suggestive of pulmonary edema and echocardiographic left ventricular dysfunction were seen [13]; (4) discontinuation of medication for COPD was identified based on the patient's history, and (5) the etiology was considered undetermined when no cause could be determined.

Clinical Data

Baseline characteristics of the patients were investigated, including age, gender, smoking history, body mass index, presenting manifestation, symptoms of respiratory infection and comorbid conditions. Pulmonary function testing was performed according to the standards of the American Thoracic Society and European Respiratory Society guidelines [14]. Available pulmonary function test data within 6 months of the index admission date were used for analysis. A subject who had smoked at least once a day for >1 year in his or her lifetime was regarded as an ever-smoker. Cumulative cigarette dose (pack-years) was calculated using the following formula: pack-years = (packs/day) × (years smoked). To assess the clinical probability of PE, we used the clinical prediction rules of the Wells score [15] and revised Geneva score [16]. Provoked PE was defined by the presence of reversible provoking risk factors including surgery, trauma, active cancer, pregnancy and puerperium within 3 months of the event or immobilization (bed rest within the past month for most of the day for ≥3 consecutive days). With regard to clinical course and outcome, the duration of the hospital stay and the rate of in-hospital mortality were recorded.

Laboratory data included acute-phase reactants such as white blood cell count, erythrocyte sedimentation rate, C-reactive protein, arterial blood gas analysis and blood biomarkers, including N-terminal-pro-B-type natriuretic peptide (NT-proBNP), troponin I, procalcitonin and D-dimer.

Radiologic Data

CT scans were performed using a multidetector CT (MDCT) with 16 or 64 detector rows (Light Speed 16, General Electric, Milwaukee, Wisc., USA, or Aquilion 64 scanner, Toshiba Medical Systems, Japan). The scan was obtained in the craniocaudal direction during a single inspiratory breath hold from the apex to the diaphragm. The CT parameters used for 16-channel MDCT were 120 kVp and a 16 × 0.75 mm collimation with a pitch of <1.5. The parameters for 64-channel MDCT were 120 kVp and 64 × 0.5 mm collimation with a pitch of <1.5. A standard dose (2 ml/kg, up to 150 ml) of low osmolar nonionic contrast media (Optiray 350, Mallinckrodt Inc., Hazelwood, Mo., USA) was injected through an arm vein at 2.5–3 ml/s. Individual optimization of peak enhancement time was achieved by using bolus tracking within the main pulmonary artery. The threshold value for triggering data acquisition was set to 250 Hounsfield units. Indirect CT venography was performed 140 s after the thoracic scan, from the diaphragm down to the ankles, to detect DVT.

As described in an earlier study [17], PE was diagnosed on CT scan as a sharply delineated pulmonary arterial filling defect present in at least two consecutive image sections and located centrally within the vessel or with acute angles at its interface with the

Table 1. VTE on CT scan

Patient No.	Most proximal site involved by PE	Most proximal site involved by DVT
1	both main pulmonary arteries	left superficial femoral vein
2	left main pulmonary artery	left superficial femoral vein
3	right main pulmonary artery	–
4	left main pulmonary artery	–
5	right interlobar and left lower lobar arteries	right popliteal vein
6	–	right popliteal vein
7	–	right posterior tibial vein
8	–	right posterior tibial vein

vessel wall. DVT was defined as a low-attenuating partial or complete intraluminal filling defect surrounded by a high-attenuating ring of enhanced blood that was seen on at least two consecutive transverse images [18]. Proximal DVT was defined as a thrombosis at the level of the popliteal vein or above and distal DVT as a thrombosis affecting the axial calf veins. We checked for the presence of consolidation or GGO, centrilobular nodules or tree-in-bud pattern, bronchiectasis, bronchial anthracofibrosis, bronchial wall thickening and pleural effusion. Each CT finding was defined as follows: consolidation as airspace opacification with obscuration of the underlying vasculature [19]; GGO as mildly increased attenuation without obscuration of the underlying vasculature [19]; tree-in-bud pattern as centrilobular nodules with either V- or Y-shaped branching linear opacities [20]; bronchiectasis when the internal diameter of the bronchus was greater than that of the adjacent pulmonary artery; bronchial anthracofibrosis as multiple smooth bronchial narrowing with adjacent calcified lymph nodes [21], and bronchial wall thickening was assessed subjectively.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 12.0 (SPSS Inc., Chicago, Ill., USA). The data are expressed as the mean $\pm$ standard deviation or median with range (maximum–minimum) if the data were skewed for continuous variables, and as a number with percentage for categorical variables. Continuous variables were compared between the two groups by the Mann-Whitney U test, whereas the categorical variables were compared using either the χ^2 test or Fisher's exact test. To search for predictors of PE, multiple logistic regression analysis was performed using variables of $p < 0.1$ in univariate analysis. The goodness-of-fit test used to assess the fit of logistic regression models was the Hosmer-Lemeshow test.

Results

Clinical Characteristics of the Patients

One hundred and seventeen patients who gave informed consent were included in the study. On the initial examination, 4 patients with pneumonia ($n = 1$), pneumothorax ($n = 2$) or congestive heart failure ($n = 1$) were excluded. Next, 8 patients with azotemia ($n = 4$) or undergo-

ing mechanical or noninvasive positive pressure ventilation ($n = 4$) were excluded before undergoing a CT scan. Lastly, 2 patients were excluded due to undetermined results of the CT scan caused by technical problems, and thus 103 patients were included in the final analysis. The mean age of the patients was 71 ± 6 years, with a male preponderance of 70% ($n = 70$). The mean percent predicted forced expiratory volume in 1 s was $58 \pm 25\%$, and the most common presenting manifestation was dyspnea (97%), followed by cough (2%) and fever (1%). The most common cause of COPD exacerbation was infection of the tracheobronchial tree (61%; $n = 63$), followed by pneumonia (20%; $n = 21$). The prevalence of PE was 5% ($n = 5$), and the frequency of the remaining causes of COPD exacerbation was as follows: congestive heart failure, 2% ($n = 2$); discontinuation of medication, 1% ($n = 1$), and undetermined etiology, 11% ($n = 11$). Thus, lower respiratory tract infection accounted for 83% ($n = 85$) of all COPD exacerbations. In 40 of the 85 cases caused by respiratory infection (47%), the causative microbes were identified. In these patients, the most frequent pathogen was *Streptococcus pneumoniae* (38%; $n = 15$), followed by *Pseudomonas aeruginosa* (23%; $n = 9$), *Klebsiella pneumoniae* (15%; $n = 6$) and *Enterobacter cloacae* (13%; $n = 5$).

The Prevalence of VTE

A total of 8 patients (8%) had VTE (table 1). The prevalence of PE in patients with COPD exacerbation was 5% ($n = 5$). The location of the proximal pulmonary emboli was central in all cases, i.e. in the right or left main pulmonary artery ($n = 4$) or interlobar-to-lobar pulmonary artery ($n = 1$). DVT was seen in 6% of patients ($n = 6$), and proximal DVT was seen in 4% ($n = 4$).

Clinical and Radiologic Features of the Patients with PE

COPD exacerbation was thought to be caused by PE in 5 patients. Four patients with pulmonary thromboem-

Table 2. Comparison of the patients with and without PE

Characteristic	PE (n = 5)	Non-PE (n = 98)	p value
Age, years	73 (69–86)	71 (49–87)	0.36
Female	3 (60)	30 (31)	0.17
Smoking status			
Ever-smoker	3 (60)	68 (69)	0.65
Never-smoker	2 (40)	30 (31)	
Pack-years	27 (15–50)	46 (2–150)	0.19
Body mass index	24 (15–31)	22 (15–39)	0.40
Spirometric data	(n = 5)	(n = 75)	
Postbronchodilator			
FEV ₁ , % predicted	50 (32–83)	57 (20–148)	0.59
FEV ₁ /FVC, %	51 (30–55)	41 (20–72)	0.58
Comorbid conditions			
Hypertension	2 (40)	24 (25)	0.44
Diabetes mellitus	0 (0)	15 (15)	0.34
Ischemic heart disease	1 (20)	5 (5)	
Malignancy	0 (0)	4 (4)	
Symptoms of respiratory infection	1 (20)	80 (83)	0.001
Increased sputum	1 (20)	68 (70)	0.02
Purulent sputum	1 (20)	55 (57)	0.11
Fever	1 (20)	36 (37)	0.44
URI symptoms	0 (0)	26 (27)	0.18
Clinical probability			
Wells score	1 (0–2)	1 (0–5)	0.84
Low	2 (5)	35 (36)	0.82
Intermediate	3 (60)	56 (57)	
High	0 (0)	7 (7)	
Revised Geneva score	5 (4–6)	5 (0–10)	0.71
Low	0 (0)	13 (13.5)	0.38
Intermediate	5 (100)	83 (86.5)	
High	0 (0)	0 (0)	
Clinical course			
Hospital stay, days	8 (2–76)	7 (0–91)	0.78
In-hospital mortality	1 (20)	5 (5)	0.26

Data are presented as medians (range) or numbers (%), as appropriate. FEV₁ = Forced expiratory volume in 1 s; FVC = forced vital capacity; URI = upper respiratory infection.

boli in either the right or left main pulmonary artery had no symptoms of respiratory infection and no other identifiable cause of COPD exacerbation. The remaining patient presented with multiple pulmonary thromboemboli in the right interlobar and left lower lobar arteries and had a sore throat and fever initially. However, while these symptoms were improving, dyspnea developed anew and was aggravated in this patient.

All patients were divided into PE (n = 5) and non-PE (n = 98) groups according to the presence of pulmonary thromboemboli on CT scan. Various clinical parameters

were compared between the two groups (table 2). Among them, the presence of symptoms of respiratory infection was significantly less commonly observed in the PE group compared to the non-PE group [20 (n = 1) vs. 83% (n = 80); p = 0.001]. No significant differences were noted with regard to the duration of hospital stay and in-hospital mortality between the two groups. Laboratory data are summarized in table 3. The serum level of NT-pro-BNP tended to be higher and the plasma D-dimer level was significantly higher in the PE compared with the non-PE group [3,182 (185–13,439) vs. 1,176 (15–16,508) pg/ml, p = 0.07, and 1,479 (427–4,041) vs. 378 (0–4,512) µg/l, p = 0.03, respectively]. When the patients were divided into two groups by a conventional D-dimer concentration cutoff point of 500 µg/l [22, 23], D-dimer elevation was significantly more common in the PE group compared with the non-PE group [75 (3/4) vs. 20% (19/88); p = 0.03]. The remaining factors, including age, gender, body mass index, spirometric data and clinical probability scores, did not differ significantly between the two groups.

The frequency of other CT findings, including consolidation or GGO (20 vs. 21%; p = 1.0), centrilobular nodules or tree-in-bud pattern (0 vs. 11%; p = 1.0), bronchiectasis (0 vs. 1%; p = 1.0), bronchial anthracofibrosis (40 vs. 38%; p = 1.0), bronchial wall thickening (0 vs. 40%; p = 0.15) and pleural effusion (20 vs. 10%; p = 0.44), did not differ between the PE and non-PE groups.

Predictors of PE in Patients with COPD Exacerbation

To identify predictors of PE as the etiology of COPD exacerbation, we performed multiple logistic regression analysis for the absence of symptoms of respiratory infection, serum NT-proBNP level and plasma D-dimer elevation (≥500 µg/l). The Hosmer-Lemeshow test indicated that the overall model fit was good (p = 0.607). Of the three variables, the absence of respiratory infection symptoms (odds ratio 31.2, 95% confidence interval 1.7–562.6; p = 0.02) and elevated plasma D-dimer level (odds ratio 25.3, 95% confidence interval 1.4–464.4; p = 0.03) were significant factors predicting PE in patients with COPD exacerbations (table 4).

Discussion

The present study demonstrated that in approximately 5% of Korean patients, COPD exacerbations resulted from PE, although data were acquired only from a single institution in South Korea. Overall, VTE was present in

Table 3. Laboratory findings of the patients with and without PE

Parameters	PE	n	Non-PE	n	p value
WBC count, / μ l	11,420 (5,090–15,520)	5	10,380 (4,240–21,640)	98	0.98
ESR, mm/h	26 (6–56)	5	31 (0–120)	90	0.73
C-reactive protein, mg/dl	1.1 (0.5–2.3)	4	4.9 (0.0–34.0)	98	0.63
Procalcitonin, ng/ml	0.05 (0.05–0.26)	3	0.05 (0.05–0.11)	74	0.95
NT-proBNP, pg/ml	3,182 (185–13,439)	5	1,176 (15–16,508)	94	0.07
CK-MB, ng/ml	2.0 (0.6–3.2)	5	3.3 (0–88)	94	0.37
Troponin I, ng/ml	0.11 (0.02–0.37)	5	0.13 (0.01–4.11)	95	0.83
D-dimer	1,479 (427–4,041)	4	378 (0–4,512)	88	0.01
>500 μ g/l	3 (75)		19 (20)		0.03
$\leq$ 500 μ g/l	1 (25)		69 (80)		
Serum albumin, g/dl	3.7 (3.3–4.1)	5	3.9 (2.2–4.9)	98	0.32
P(A-a)O ₂ , mm Hg	126 (96–184)	4	124 (20–508)	98	0.77
PaCO ₂ , mm Hg	45 (64–67)	4	39 (7–104)	98	0.27
PaO ₂ , mm Hg	79 (71–86)	4	83 (23–532)	98	0.68

Data are presented as medians (range) or numbers (%), as appropriate. WBC = White blood cell; ESR = erythrocyte sedimentation rate; CK-MB = creatine kinase-MB; P(A-a)O₂ = alveolar-arterial oxygen difference; PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension.

8% of patients, and DVT was seen in 6%, with proximal DVT in 4%. The absence of respiratory infection symptoms and elevated plasma D-dimer level are significant factors in predicting PE in patients with COPD exacerbations. Additionally, CT scan may contribute to the diagnosis of lower respiratory tract infection, including pneumonia and tracheobronchitis.

Considering all studies using pulmonary angiography and CT pulmonary angiography, the prevalence of PE as the etiology of COPD exacerbation is variable, ranging from 3.3 to 29%, depending on whether the study population included patients with respiratory infection [6–8, 24, 25]. In three studies using MDCT, the prevalence of PE was 25% in a report in patients with only an unknown etiology [6], whereas when patients with respiratory infection were included, the rate of PE was 3.3% in one study [7] and 14% in the other study [8]. The study population of the present study was similar to those of the latter two studies. We suggest that the very low prevalence in the study by Rutschmann et al. [7] was due to the study protocol, in which subjects with a plasma D-dimer value <500 μ g/l were excluded. In the current study, 1 of 4 patients with available D-dimer results had a plasma level of D-dimer <500 μ g/l. The other study reported a higher prevalence (14%) than our study [8]. Considering the ethnic difference that VTE is less common in Asians compared with Caucasian and African-American patients, the prevalence of PE in our study is plausible. Similarly, the prevalence of DVT (8%) was lower in the present

Table 4. Multivariate analysis for predictors of PE

Predictor	Odds ratio	95% CI	p value
Plasma D-dimer >500 μ g/l	25.3	1.4–464.4	0.03
Absence of symptoms of respiratory infection	31.2	1.7–562.6	0.02
Level of NT-proBNP	0.99	0.99–1.00	0.19
CI = Confidence interval.			

study compared to the rate (11%) reported by Gunen et al. [8]. In addition, if the patients in our study with respiratory infection, including tracheobronchitis and pneumonia, were excluded, the prevalence of PE was 26% (5/19). This value is very similar to that reported by Tillie-Leblond et al. [6].

Additional information, as well as PE, was obtained from MDCT data in our study. There was no statistically significant difference with regard to other CT findings, such as consolidation or GGO, bronchiolitis, diffuse bronchial wall thickening or pleural effusion, between the PE and non-PE groups. However, MDCT was helpful to find other causes of COPD exacerbation, including pneumonia and tracheobronchitis. On CT scan, 21 patients whose chest radiographs were not conclusive were identified as having pneumonic consolidation or GGO, and bronchiolitis was also identified in 11 patients. It is

uncertain whether these additional findings were of assistance with respect to the therapeutic plan and prognosis.

What kind of factors can predict PE in patients with COPD exacerbation? Traditional clinical probability scores were not useful in predicting the presence of PE in the current study. From our results, the absence of symptoms suggestive of respiratory infection and elevated plasma D-dimer level can be used as predictors. A previous study [8] to predict VTE in patients presenting with COPD exacerbation did not reveal any significant parameters. Nevertheless, they insisted that a low D-dimer level was the single most useful hematological parameter for excluding VTE.

The present study has several limitations. Although the patients were enrolled prospectively, some laboratory data and pulmonary function test results within 6 months from the index day were not available. Thus, selection bias could not be avoided. Secondly, as our criteria for

tracheobronchitis and pneumonia were broad, the possibility that the true prevalence of these two etiologies was overestimated cannot be excluded. However, we believe that this did not influence our primary purpose to determine the prevalence and predictors of PE in Korean patients with COPD exacerbations. Lastly, the number of patients with PE was so small that other clinical parameters predicting PE might have been missed.

In conclusion, PE comprises approximately 5% of the etiologies of COPD exacerbations in Koreans. The absence of symptoms suggestive of respiratory infection and elevated plasma D-dimer level were significant predictors of PE in these patients.

Financial Disclosure and Conflicts of Interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

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