Thorac Res Pract. 2024; 25(2): 57-61 DOI: 10.5152/ThoracResPract.2024.23097

Original Article

Assessing the Prevalence of Pulmonary Embolism and the Clot Burden in Hospitalized Patients with Chronic Obstructive Pulmonary Disease Exacerbation

Neda Akhoundi[1], Mahlagha Amirbakhtiarvand[2], Mobina Goli[2], Zahra Naseri[3], Alireza Siami[4]

[1]Department of Radiology, Hillcrest Hospital, University of California San Diego, San Diego, CA, USA
[2]Islamic Azad University School of Medicine, Shahroud, Iran
[3]Department of Radiology, Shahid Beheshti University of Medical Science, Tehran, Iran
[4]Biostatistical Analyzer, Amirkabir University of Technology, Tehran, Iran

Cite this article as: Akhoundi N, Amirbakhtiarvand M, Goli M, Naseri Z, Siami A. Assessing the prevalence of pulmonary embolism and the clot burden in hospitalized patients with chronic obstructive pulmonary disease exacerbation. *Thorac Res Pract.* 2024;25(2):57-61.

Abstract

OBJECTIVE: This prospective cohort study aimed to assess the pulmonary embolism (PE) rate and clot burden in patients with chronic obstructive pulmonary disease (COPD) exacerbation.

MATERIAL AND METHODS: A total of 248 patients entered the study, and their clinical probability of PE was assessed using the Geneva score. Patients with high clinical probability underwent computed tomographic pulmonary angiography, while those with low or intermediate probability underwent a D-dimer test.

RESULTS: Among the patients analyzed, 14 individuals (5.6%) were confirmed to have PE using computed tomographic pulmonary angiography. A 3-month follow-up revealed 3 cases of PE out of 232 patients initially deemed PE-free. Mortality rates were higher among patients with venous thromboembolism at admission than those diagnosed with PE during follow-up. Pulmonary embolism (PE) prevalence among patients with COPD exacerbation was 5.6%.

CONCLUSION: The results of this study show the importance of screening for PE in patients with COPD presenting with dyspnea. Not all of them are due to COPD exacerbation; a small minority of them can be due to PE, which needs prompt screening, confirmation, and therapy. However, further research with larger cohorts is required to understand better the potential benefits and implications of systematic screening for pulmonary embolism in this specific patient population.

KEYWORDS: Qanadli index, embolism, pulmonary CT angiography

Received: *August 29, 2023* ***Revision Requested:*** *October 30, 2023* ***Last Revision Received:*** *November 1, 2023*
Accepted: *December 18, 2023* ***Publication Date:*** *February 8, 2024*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory condition characterized by persistent airflow constriction and gradual lung function deterioration. It leads to substantial sickness and loss of life annually. The fatality linked to COPD is impacted by sudden worsening episodes known as acute exacerbations, necessitating alterations in treatment due to sudden respiratory symptom aggravation.[1]

Triggers of these acute COPD exacerbations encompass multiple factors, including bronchial infections and exposure to air pollutants. Intriguingly, several investigations have indicated a notable prevalence of pulmonary embolism occurrences in patients undergoing COPD exacerbations.[2-5] A comprehensive analysis found that approximately 16% of hospitalized patients encountering unexplained acute COPD exacerbations simultaneously suffered from pulmonary embolism. Furthermore, a retrospective assessment disclosed that regardless of the initial suspected cause of exacerbation, pulmonary embolism emerged as the primary cause of fatality in 21% of patients admitted for acute COPD exacerbations.[6,7] The connection between exacerbations of COPD and the occurrence of pulmonary embolism poses a complex clinical situation, given that the symptoms of both conditions can overlap, leading to challenges in diagnosis and possible delays in appropriate treatment. However, determining the most effective approach for screening and diagnosing pulmonary embolism in hospitalized patients experiencing acute COPD exacerbation remains a formidable task. The current diagnostic methods employed for suspected acute pulmonary embolism in the general population might not yield the same results when applied to COPD exacerbations, particularly in the context of ventilation–perfusion lung scans. Furthermore, the clinical manifestations of acute pulmonary embolism and COPD exacerbation exhibit similarities, complicating the decision of whether pulmonary embolism should be considered in this specific clinical scenario.[8,9]

It is crucial to establish the precise frequency of pulmonary embolism among patients undergoing COPD exacerbation in order to enhance patient care and outcomes. This study, conducted with prospective follow-up, aimed primarily to

Corresponding author: Neda Akhoundi, e-mail: nakhoundi@health.ucsd.edu

determine the prevalence of pulmonary embolism in COPD patients admitted to the hospital due to sudden worsening of respiratory symptoms. Additionally, we aimed to evaluate the extent of clot presence through pulmonary CT angiography.[10,11] Our intention is to raise health-care professionals' awareness about the concealed risk of pulmonary embolism in cases of COPD exacerbations, prompting them to remain vigilant and factor in this potential complication when assessing patients with abruptly deteriorating respiratory symptoms.

MATERIAL AND METHODS

Ethical Review and Study Organization

The Ethics Committee of IAU (Approval number: 9716, Date: July 25, 2017) approved our prospective cohort study. Informed consent was obtained. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Study Participants

From September 2017 to December 2022, a continuous series of adult outpatients (18 years or older) were enrolled to the teaching hospital due to sudden worsening of respiratory symptoms associated with COPD. To confirm the COPD diagnosis, patients were required to show either previous pulmonary function test results indicating a post-bronchodilator forced expiratory volume in the first second of expiration to forced vital capacity ratio of less than 70%, or a COPD diagnosis previously established by a pulmonologist. The criteria for defining acutely worsening respiratory symptoms in COPD encompassed a sustained deterioration in the patient's typical symptoms (such as dyspnea, cough, and sputum production) beyond the expected day-to-day fluctuations, necessitating an alteration in treatment.

Exclusion criteria consisted of individuals with contraindications for undergoing computed tomographic pulmonary angiography (specifically those with a known allergy to iodine contrast agents), a creatinine clearance level below 30 mL/min/1.73 m² (indicative of severe kidney impairment), pregnancy, hospitalization exceeding 48 hours before inclusion, and anticoagulant therapy administered for reasons unrelated to venous thromboembolism**.**

Pulmonary Embolism Diagnostic Procedure

Patients were enrolled within 48 hours of being admitted to the hospital and categorized based on whether they displayed clinically suggestive symptoms of pulmonary embolism or not, as well as whether an alternative diagnosis more or less likely than pulmonary embolism was established.

The clinical likelihood of pulmonary embolism was evaluated for all patients using the Geneva score.[12] Patients with a high clinical likelihood (defined as a Geneva score ≥11) underwent computed tomographic pulmonary angiography. For patients with a low or moderate clinical likelihood (Geneva score <11), a D-dimer test was conducted and interpreted using the standard threshold of 500 ng/mL, denoted as Fibrinogen Equivalent Units. In cases where the D-dimer test yielded a negative result, the presence of pulmonary embolism was ruled out, and no further testing was conducted.

Follow-up visits were conducted monthly over a period of 3 months to identify any indications of venous thromboembolism.

Pulmonary Computed Tomography Angiography

Chest CT scans were performed using a multidetector CT scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio, USA). The scan slice thickness was configured at 1mm with a 0.5 mm increment. For CT angiography, a total of 50ml of iodinated contrast material (Visipaque 320 mm iodine/mL) was administered intravenously, and scans were captured at the end of an inhalation during a single breath-hold. Two radiologists with 14 and 17 years of experience in interpreting thoracic CT scans evaluated the images. These radiologists evaluated the images without access to the patient's medical history, ensuring impartial assessment.

For patients diagnosed with pulmonary embolism (PE), the pulmonary artery obstructive index (Qanadli index) was calculated based on the degree of involvement of pulmonary arterial branches.

The primary objective of the study was to identify cases of pulmonary embolism within the initial 48 hours of admission. Diagnosis of pulmonary embolism was confirmed by detecting the presence of acute thrombosis within the lumen of the pulmonary arterial tree using computed tomographic pulmonary angiography.

A significant secondary outcome concentrated on observing instances of pulmonary embolism during the 3-month tracking period in patients who were initially determined to be free of venous thromboembolism within the first 48 hours of hospital admission.

Statistical Analysis

Descriptive statistics were presented as mean ± SD for continuous variables and as numbers (percentages) for categorical variables. Comparisons between means of continuous variables were conducted using either an independent group *t*-test or the Mann–Whitney U-test. The chi-square test was employed to compare the proportions of categorical variables. The association between quantitative variables was examined using either Pearson's or Spearman's correlation tests. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA), with a significance level set at $P < .05$.

Main Points

- The clinical manifestations of acute pulmonary embolism and chronic obstructive pulmonary disease (COPD) exacerbation exhibit similarities, complicating the decision of whether pulmonary embolism should be considered in this specific clinical scenario.
- A total of 5.6% of the patients with the symptoms of COPD exacerbation were diagnosed with pulmonary embolism.
- Mean main pulmonary artery diameter was higher in patients with COPD and pulmonary embolism in the mortality group compared to the survivors.

RESULTS

In the present study, a total of 286 patients with COPD and acutely worsened respiratory symptoms were admitted to the hospital and screened for potential participation. However, 21 patients were excluded from the study due to being on long-term anticoagulation therapy and 17 patients were excluded because of being unable to provide informed consent. Finally, 248 patients entered the study.

The baseline characteristics of the patients are summarized in Table 1. These patients had a mean age of 67.3 years (SD of 10.4 years), and among them, 93 were women (34.0% of the total sample). Based on the Geneva score, out of the 248 patients analyzed in the study, 130 patients (52%) had a low score. Additionally, 112 patients (45%) had an intermediate score, while 6 patients (2%) had a high score (Table 1).

Table 1. Basic Characteristics of Patients

Variables	n (%) (n = 248)
Age, mean (SD), years	67.3 (10.4)
Women	93 (34.0%)
FEV1, % predicted	0.59 (0.95)
FEV1/FVC, %	54 (16.9)
Active tobacco use	223 (89%)
Geneva score	
Low	130 (52%)
Intermediate	112 (45%)
High	6 (2%)
Heart rate >110/min	52 (21%)
Use of accessory inspiratory muscles	49 (20%)
Neurological impairment	10 (4%)
Cyanosis	37 (15%)
Bilateral lower limb edema	69 (27.8%)
Oxygen therapy required	119 (47.9%)

Primary Outcome

Among the 248 patients included in the study, 6 patients (2.4%) were classified as having a high pretest clinical probability according to the Geneva score. Among these 6 patients, pulmonary embolism was confirmed in 4 patients through spiral computed tomographic pulmonary angiography.

For the remaining 242 patients with a low or moderate pretest clinical probability, a D-dimer assay was conducted. Among these patients, 173 individuals had D-dimer levels lower than 500 µg/mL, and pulmonary embolism was considered excluded without further diagnostic work-up. Among the 69 patients with positive D-dimer test results, 68 patients underwent spiral computed tomographic pulmonary angiography. Out of these 68 patients, 10 were confirmed to have pulmonary embolism. In total, among the 248 included patients, pulmonary embolism was confirmed in 14 patients, resulting in a prevalence of 5.6% (95% CI, 4.2%-8.1%) (Figure 1).

Three-Month Follow-up

During the 3-month follow-up period, among the initial 234 patients who were determined to be free of pulmonary embolism, 2 patients were lost to follow-up, leaving a total of 232 patients available for further evaluation. Over the course of the follow-up, 3 out of the remaining 232 patients were diagnosed with pulmonary embolism. The study also disclosed mortality rates for patients with venous thromboembolism (VTE) at admission and those diagnosed with pulmonary embolism during the 3-month follow-up. Among the patients with VTE at admission, the mortality rate was 3 out of 14 patients (25.1%). In contrast, among those patients diagnosed with pulmonary embolism during the follow-up period, 1 out of 3 patients (5.1%) experienced mortality.

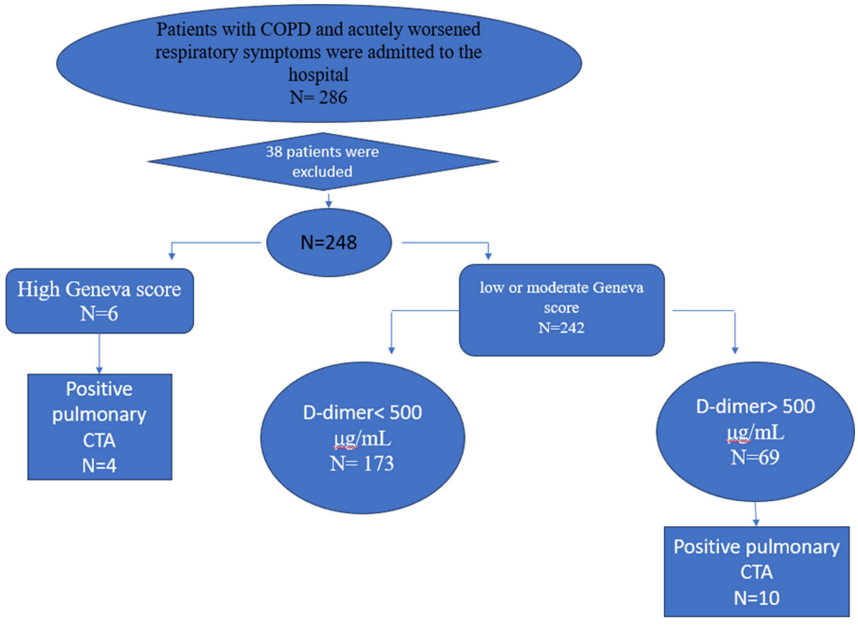

Figure 1. Flowchart showing the patients' entry into the study and their investigation results.

Table 2. Comparison of Quantitative and Qualitative Characteristics of Patients with Pulmonary Embolism Among Subgroups of Mortality and Survivors in Patients with Chronic Obstructive Pulmonary Disease

Object	Mortality Group (n = 4)	COPD Patients with PE Who Survived (n = 13)	*P*
Age, years, median (25-75th percentiles)	64 (61-75)	58 (46-73)	.300
Gender (Male)	2 (50%)	7 (54%)	.484
PAOI	13 (9-24)	4 (2-13)	.002
MPA diameter (mm)	30.5 ± 3.4	26.6 ± 2.6	.003
Aorta diameter (mm)	32.4 ± 3.5	31.3 ± 3.3	.078
MPA/aorta ratio	0.91 ± 0.13	0.65 ± 0.14	.039
Level of thrombosis			
MPA	1 (33%)	0 (0%)	.651
RPA	1 (33%)	0 (0%)	.655
LPA	0 (0%)	0 (0%)	N/A
Lobar artery	2 (66%)	5 (38%)	.093
Segmental artery	3 (100%)	6 (46%)	.225
Subsegmental artery	3 (100%)	2 (15%)	.06

COPD, chronic obstructive pulmonary disease; LPA, left pulmonary artery; MPA, main pulmonary artery; N/A, not applicable; PAOI, pulmonary artery obstruction index; PE, pulmonary embolism; RPA, right pulmonary artery.

Furthermore, the investigation assessed the average pulmonary artery obstruction index (PAOI) based on the Qanadli score in patients with pulmonary embolism. In the patients who suffered mortality, the mean PAOI was 13, while among the survivors, the mean PAOI was 4. This discrepancy was found to have statistical significance, with a *P*-value of 0.002. Similarly, the mean diameter of the main pulmonary artery (MPA) in the mortality group measured 30.5 ± 3.4 mm, which was higher than that of the survivors (26.6 ± 2.6 mm). This difference also exhibited statistical significance, with a *P*-value of 0.003, as indicated in Table 2.

DISCUSSION

This cohort study observed 248 patients with COPD who were hospitalized due to COPD exacerbation. Within 48 hours of their admission, an evaluation was conducted to detect the presence of pulmonary embolism. The findings demonstrated that 5.6% of the patients were diagnosed with pulmonary embolism. Among the initial 234 patients identified as not having venous thromboembolism at the outset of the study, 1.2% of them eventually developed pulmonary embolism.

The prevalence of pulmonary embolism in this specific study (5.6%), focusing on COPD patients admitted to the hospital, was observed to be lower in comparison to a meta-analysis that reported a higher prevalence of 16.1%.[13] This discrepancy could be attributed to the diversity observed across various studies. These variations encompass differences in diagnostic approaches for pulmonary embolism, methodologies used for COPD assessment, and disparities within the study populations.[3]

The utilization of imaging for the assessment of various medical conditions is widely recognized.[14-19] This study stands apart from preceding research due to its distinctive investigation involving pulmonary CT angiography to evaluate clot burden in COPD patients. To the best of our knowledge, this study constitutes the largest cohort analysis aimed at appraising the PAOI in documented COPD patients concurrently affected by PE. A notable strength of this study is its meticulous process for validating instances of pulmonary embolism.[20] The study provides a dependable approximation of pulmonary embolism prevalence within the particular context under scrutiny. The observed prevalence of pulmonary embolism among patients with suspected cases upon admission aligns with rates seen in recent studies encompassing a broader spectrum of outpatients with suspected pulmonary embolism. This concurrence in prevalence implies that the study's findings harmonize with outcomes from earlier investigations conducted among distinct patient groups, thereby fortifying the credibility of the prevalence estimation rendered by this study.[21,22] The study reveals a 4% prevalence of venous thromboembolism (VTE) for patients initially lacking clinical suspicion of pulmonary embolism. This finding underscores the significance of not overlooking VTE as insignificant within this subgroup. As a result, the study prompts a pertinent question concerning the necessity for systematic screening for pulmonary embolism even in patients initially lacking suspicion.[7,23-25] This study has some limitations. First of all, the study has been conducted in only 1 center. Secondly, while the study comprises a large cohort and holds value, it is important to note that generalizations cannot be made. Therefore, it is necessary to conduct a clinical study that would yield higher levels of evidence.

The results of this study show the importance of screening for PE in patients with COPD presenting with dyspnea. Not all of them are due to COPD exacerbation; a small minority of them can be due to PE, which needs prompt screening, confirmation, and therapy. However, further research with larger

cohorts is required to understand better the potential benefits and implications of systematic screening for pulmonary embolism in this specific patient population.

Ethics Committee Approval: The study was approved by the medical ethics committee of IAU (Approval No: 97169716, Date: July 25, 2017). This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.A., Z.N.; Design – Z.N., M.A.; Supervision – M.A., M.G.; Resources – M.A., Z.N.; Materials – M.A., M.G.; Data Collection and or Processing – M.A., M.G.; Analysis and/or Interpretation – A.S.; Literature Search – M.A., M.G.; Writing – N.A., Z.N.; Critical Review – M.A., M.G.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J*. 2019;53(5):1900164. [CrossRef]
2. Sapey E, Stockley RA. COPD exacerbations, 2: etiology. *Thorax*. 2006;61(3):250-258. [CrossRef]
3. Tillie-Leblond I, Marquette CH, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med*. 2006;144(6):390-396. [CrossRef].
4. Akpinar EE, Hoşgün D, Akpinar S, Ataç GK, Doğanay B, Gülhan M. Incidence of pulmonary embolism during COPD exacerbation. *J Bras Pneumol*. 2014;40(1):38-45. [CrossRef]
5. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*. 2009;135(3):786-793. [CrossRef]
6. Zvezdin B, Milutinov S, Kojicic M, et al. A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest*. 2009;136(2):376-380. [CrossRef]
7. Bertoletti L, Quenet S, Mismetti P, et al. Clinical presentation and outcome of venous thromboembolism in COPD. *Eur Respir J*. 2012;39(4):862-868. [CrossRef]
8. Hartmann IJ, Hagen PJ, Melissant CF, Postmus PE, Prins MH, ANTELOPE Study Group. Diagnosing acute pulmonary embolism: Effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. ANTELOPE Study Group. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism. *Am J Respir Crit Care Med*. 2000;162(6):2232-2237. [CrossRef]
9. Akhoundi N, Sedghian S, Siami A, et al. Does adding the pulmonary infarction and right ventricle to left ventricle diameter ratio to the Qanadli index (a combined Qanadli index) more accurately, predict short-term mortality in patients with pulmonary embolism? *Indian J Radiol Imaging*. 2023;33(4):478-483. [CrossRef]
10. Akhoundi N, Faghihi Langroudi T, Rajebi H, et al. Computed tomography pulmonary angiography for acute pulmonary embolism: prediction of adverse outcomes and 90-day mortality in a single test. *Pol J Rad*. 2019;84:436-446.
11. Akhoundi N, Faghihi Langroudi T, Rezazadeh E, et al. Role of clinical and echocardiographic findings in patients with acute pulmonary embolism: prediction of adverse outcomes and mortality in 180 days. *Tanaffos*. 2021;20(2):99-108.
12. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: The revised Geneva score. *Ann Intern Med*. 2006;144(3):165-171. [CrossRef]
13. Aleva FE, Voets LWLM, Simons SO, de Mast Q, van der Ven AJAM, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: A Systematic Review and Meta-analysis. *Chest*. 2017;151(3):544-554. [CrossRef]
14. Akhoundi N, Faghihi Langroud T, Shafizadeh K, Jabbarzadeh MJ, Talebi S. Incidental abdominal aortic aneurysm in the psoriasis patient: a case report and review of literature. *Galen Med J*. 2018;7:e1168. [CrossRef])
15. Sepideh H, Shahram K, Arda K, et al. The diagnostic accuracy of endobronchial ultrasound and spiral chest computed tomography scan in the prediction of infiltrating and non-infiltrating lymph nodes in patients undergoing an endobronchial ultrasound. *Pol J Rad*. 2019;84:565-569.
16. Akhoundi N, Bozchelouei JK, Abrishami A, et al. Comparison of MRI and endoanal ultrasound in assessing intersphincteric, transsphincteric, and suprasphincteric perianal fistula. *J Ultrasound Med*. 2023;9999:1-8. [CrossRef])
17. Nosrati M, Akhoundi N, Ahmadzadeh Nanva AH, et al. The role of lung ultrasonography scoring in predicting the need for surfactant therapy in neonates, with respiratory distress syndrome. *J Diagn Med Sonogr*. 2023;39(4):348-354. [CrossRef])
18. Akhoundi N, Rezazadeh E, Siami A, Komijani Bozchelouei J, Ramezani M, Nosrati M. The comparison of pulsatility index, resistance index, and diameter of the temporal, carotid, and vertebral arteries during active migraine headaches to non-headache intervals. *J Diagn Med Sonogr*. 2023;39(5):442-449. [CrossRef])
19. Paraham M, Momeni Moghadam A, Akhoundi N, Haghi S. An investigation of the relationship between vitamin D deficiency and carotid intima-media thickness (IMT) in patients with Type 1 diabetes. J Pharm Neg Results. 2022:8033-8039.
20. Konstantinides SV, Meyer G, Becattini C, et al.; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603. [CrossRef])
21. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354(22):2317-2327. [CrossRef])
22. Kearon C, de Wit K, Parpia S, et al. Diagnosis of Pulmonary Embolism with D-dimer adjusted to clinical probability. *N Engl J Med*. 2019;381(22):2125-2134. [CrossRef])
23. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *Eur Respir J*. 2010;35(6):1243-1248. [CrossRef])
24. Carson JL, Terrin ML, Duff A, Kelley MA. Pulmonary embolism and mortality in patients with COPD. *Chest*. 1996;110(5):1212-1219. [CrossRef])
25. Lee AY, Rickles FR, Julian JA, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. *J Clin Oncol*. 2005;23(10):2123-2129. [CrossRef])