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Systematic review

Missed Diagnosis of Pulmonary Embolism in Patients Presenting with Acute Exacerbation of COPD: A Systematic Review

Hisham Alyahya[1], Ibrahim Abdulaziz Alqunayah[2], Raghad M. Alanazi[3], Tamam Abdulrahman Aldaham[4], Khulud Edris Mohamed[5], Nirouz Arif Hindawi[6], Ali Ibrahim Alabdullatif[7], Ayad Khalid A. Almetairi[8], Anas Abdulrahman Bahassan[9], Mohammad Hussain Alamoudi[10], Shahad Khaled Otaibi[11]

1. Emergency Medicine Consultant, Emergency Department, Riyadh First Health Cluster, Riyadh, Saudi Arabia. Email: hfiy.hf@gmail.com
2. Medical Intern, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia. Email: abra.abdulaziz1@gmail.com
3. Medical Intern, College of Medicine, Najran University, Najran, Saudi Arabia. Email: raghadalanazi.ra@gmail.com
4. Medical Intern, College of Medicine, Al-Jouf University, Sakaka, Saudi Arabia. Email: t.aldaham0@gmail.com
5. Medical Intern, Kasr Al Ainy Faculty of Medicine, Cairo University, Cairo, Egypt. Email: Khloudib1@gmail.com
6. General Physician, College of Medicine, Sulaiman Alrajhi University, Al-Qassim, Saudi Arabia. Email: hendawinirouz@gmail.com
7. General Physician, College of Medicine, Sechenov University, Moscow, Russia. Email: Ali.abdulattif@gmail.com
8. Medical Intern, College of Medicine, Al-Rayan National Colleges, Al-Madinah, Saudi Arabia. Email: ayad.khalid@hotmail.com
9. Medical Intern, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia. Email: anas.bahassan2001@gmail.com
10. Medical Intern, Kasr Al Ainy Faculty of Medicine, Cairo University, Cairo, Egypt. Email: M7md_7i@icloud.com
11. Medical Intern, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. Email: Otaibishahad9@gmail.com

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10/11/2026

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Abstract

Background: Pulmonary embolism presents with symptoms that overlap with acute exacerbation of chronic obstructive pulmonary disease, creating uncertainty about its frequency and initial recognition during routine assessment. This review examined prevalence, unsuspected disease, and associated clinical features. **Methods:** Original studies published through 31 May 2026 were examined using a framework that separated systematically detected embolism, initially unsuspected embolism, and diagnoses established after the initial assessment. Findings were synthesized narratively because recruitment criteria, diagnostic pathways, and outcome definitions differed. **Results:** We included eleven primary studies and three secondary analyses. Pulmonary embolism prevalence ranged from 3.3% to 29.1% in prospective investigations, while a large emergency department database recorded diagnosed embolism in 0.56% of presentations. In patients without initial clinical suspicion, individual studies reported embolism in 1.3% and 4.6%, respectively. Associated features included previous venous thromboembolism, malignancy, reduced arterial carbon dioxide, absent infectious symptoms, obesity, lower limb asymmetry, and tachypnoea. Several associations originated from small samples, and subsequent prediction models showed limited discrimination or required further prospective evaluation. Routine active investigation did not improve the primary composite clinical outcome in the randomised trial. **Conclusion:** Pulmonary embolism represents an established alternative or accompanying diagnosis during COPD exacerbations, mainly in selected unexplained presentations. Available data support careful risk assessment without equating screening prevalence with the prevalence of missed diagnosis.

Keywords: Pulmonary embolism; chronic obstructive pulmonary disease; acute exacerbation; missed diagnosis; prevalence; predictors.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) involve worsening respiratory symptoms over a short period, with clinical severity determined by changes in symptoms, physiological measurements, and inflammatory findings rather than the presenting complaint alone (1). Patients presenting with this pattern frequently have coexisting conditions, including pneumonia, heart failure, arrhythmia, and pulmonary embolism (PE), which complicate the attribution of acute breathlessness to an airway exacerbation. An initial diagnosis of acute exacerbation of COPD (AECOPD) does not establish the underlying cause of deterioration in each patient, and the assessment requires attention to alternative conditions that resemble or accompany the respiratory presentation (2).

Earlier estimates of PE prevalence varied, with the meta-analysis by Rizkallah et al. reporting an overall prevalence of 19.9% across studies that differed in recruitment setting and diagnostic investigation (3). Aleva et al. reported a pooled prevalence of 16.1% among patients with unexplained exacerbations, indicating that recruitment restricted to presentations without an established cause identifies a population with substantial thromboembolic disease (4). A later synthesis of 16 studies reported a prevalence of 12%, accompanied by considerable statistical heterogeneity, demonstrating that a single pooled estimate does not describe every emergency or inpatient COPD population equally (5).

Diagnostic uncertainty involves the interpretation of laboratory investigations, since a positive D-dimer result has limited specificity and requires assessment alongside clinical probability and an appropriate confirmatory imaging pathway. The Cochrane diagnostic review identified high sensitivity across the included studies alongside frequent false-positive results, particularly in older patients, illustrating the limitations of treating an elevated concentration as evidence of established embolism (6). These considerations are relevant to acute COPD care because patients present with overlapping symptoms and multiple competing diagnoses, creating a need to interpret diagnostic findings within the wider clinical assessment (2,6).

A further distinction concerns the meaning of missed diagnosis, since PE found through systematic investigation after an exacerbation presentation does not itself demonstrate an earlier

10/11/2026

diagnostic error or a preventable delay in recognition (2,4,5). Reporting recommendations for systematic reviews require explicit eligibility criteria, clearly defined outcomes, and a transparent description of how evidence was selected and synthesised, which are particularly relevant when related diagnostic outcomes have different meanings (7). This review examined PE prevalence during AECOPD, data of initially unsuspected disease, and reported clinical predictors, while separating these findings from documented diagnostic delay and considering the implications for assessment in emergency and inpatient settings.

Methods

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 framework and addressed PE in adults presenting with AECOPD. PubMed, Scopus, and Web of Science were searched from inception through 31 May 2026, with Cochrane reviews consulted for background and reference identification. Eligibility covered observational studies and randomised trials reporting PE prevalence, initial clinical suspicion, diagnostic timing, or predictors in an identifiable acute COPD population.

Search concepts combined COPD, chronic obstructive pulmonary disease, chronic bronchitis, and emphysema with pulmonary embolism, pulmonary thromboembolism, and venous thromboembolism. Exacerbation, acute deterioration, hospital admission, and emergency presentation terms were added where appropriate, while missed diagnosis and delay terms were not mandatory because relevant prevalence studies rarely used that terminology. Database-specific subject headings, free-text terms, and reference-list searches were used, with publication dates restricted to the review cutoff.

Two authors independently screened titles and abstracts, reviewed potentially eligible full texts, and extracted study information, resolving disagreements through discussion. Eligible reports included adults with established or clinically diagnosed COPD assessed during acute respiratory deterioration, with an explicit diagnostic pathway and extractable PE findings. Case reports, editorials, protocols, stable COPD cohorts, and studies without separable acute COPD results were excluded from the primary evidence synthesis.

Extraction covered study location, design, recruitment criteria, sample size, diagnostic tests, timing, initial suspicion, PE frequency, associated variables, and clinical outcomes. Three outcomes were distinguished, PE detected during the exacerbation episode, PE detected despite absent initial suspicion, and PE diagnosed after an earlier negative or incomplete assessment. PE without initial suspicion was treated as unrecognised disease rather than proof of diagnostic error, and predictor analyses compared participants with and without embolism. Diagnoses during follow-up were retained separately because the available information did not consistently distinguish incident thrombosis from disease present at the index assessment.

Methodological assessment examined participant selection, diagnostic verification, completeness of follow-up, outcome definitions, and adjustment for confounding, with additional attention to randomisation and outcome assessment in the trial. Each prevalence denominator reflected the population evaluated under the reported diagnostic strategy for each individual diagnostic endpoint. Reported risk ratios and odds ratios were preserved with their original CIs, and adjusted estimates were distinguished from unadjusted associations. Findings were analyzed qualitatively by recruitment setting and diagnostic strategy; secondary analyses were linked to their parent cohorts to avoid duplicate counting, and no combined missed-

10/11/2026

diagnosis prevalence was calculated because the studies did not share a diagnostic-error definition.

Results

Tillie-Leblond et al. identified PE in 49 of 197 patients with severe unexplained exacerbations, corresponding to 24.9%, and reported associations with previous thromboembolism, malignancy, and a reduction in arterial carbon dioxide (8). Rutschmann et al. found PE in 4 of 123 emergency presentations, including one case among 75 patients without initial suspicion, which corresponded to an unsuspected prevalence of 1.3% (9). Gunen et al. detected PE in 18 of 131 hospitalised patients, while the reported association between unexplained exacerbation and thromboembolism concerned the broader venous thromboembolism outcome (10).

Choi et al. diagnosed PE in 5 of 103 patients, with absent respiratory infection symptoms and elevated D-dimer independently associated with PE, although confidence intervals were wide (11). Akpinar et al. reported 50 PE diagnoses among 172 patients, giving the highest prevalence in this group of prospective studies at 29.1%, with obesity and lower limb asymmetry retained as independent predictors (12). Shapira-Rootman et al. diagnosed PE in 9 of 49 patients and reported one affected patient with a normal D-dimer, illustrating the limitations of isolated biomarker interpretation in a small cohort (13).

Chaudhary et al. found PE in 14 of 100 unexplained exacerbations, with respiratory alkalosis associated with PE in multivariable analysis (14). The French PEP investigation identified PE in 44 of 740 patients, or 5.9%, and reported a 4.3% prevalence of venous thromboembolism among patients without initial PE suspicion, an outcome that included deep venous thrombosis (15). In SLICE, active investigation identified PE in 17 of 370 patients without initial suspicion, or 4.6%, and the primary 90-day composite outcome occurred in 29.7% versus 29.2% with usual care (16).

Liu et al. reported PE in 266 of 1,580 hospitalised patients, corresponding to 16.8%, while the broader venous thromboembolism outcome affected 387 patients, confirming the importance of maintaining separate outcome denominators (17). Rowe et al. recorded 68 PE diagnoses among 12,164 emergency presentations, including 27 diagnoses established during hospitalisation after the emergency assessment, with only 17% receiving any investigation for PE (18). This administrative cohort measured diagnosed disease under routine practice, and the later inpatient diagnoses lacked the individual adjudication required to establish that PE had been missed during the preceding assessment (18).

Secondary analysis of PEP and SLICE data identified a respiratory rate of at least 30 breaths/min as an independent predictor, with an adjusted odds ratio of 2.77, while overall model discrimination remained limited (19). A COPD-specific strategy derived from 734 PEP participants and externally assessed in SLICE reported a 0.9% diagnostic failure rate, using clinical features and differentiated D-dimer thresholds for PE or proximal DVT (20). Another SLICE analysis found that age-adjusted D-dimer interpretation increased negative classifications from 49.5% to 63.3%, while sensitivity declined from 94.1% to 76.5%, demonstrating a trade-off between fewer investigations and false-negative results (21). The eleven primary studies represented distinct populations, whereas these three later analyses reused PEP or SLICE participants and were treated as supplementary evidence rather than additional independent cohorts of patients (19-21).

10/11/2026

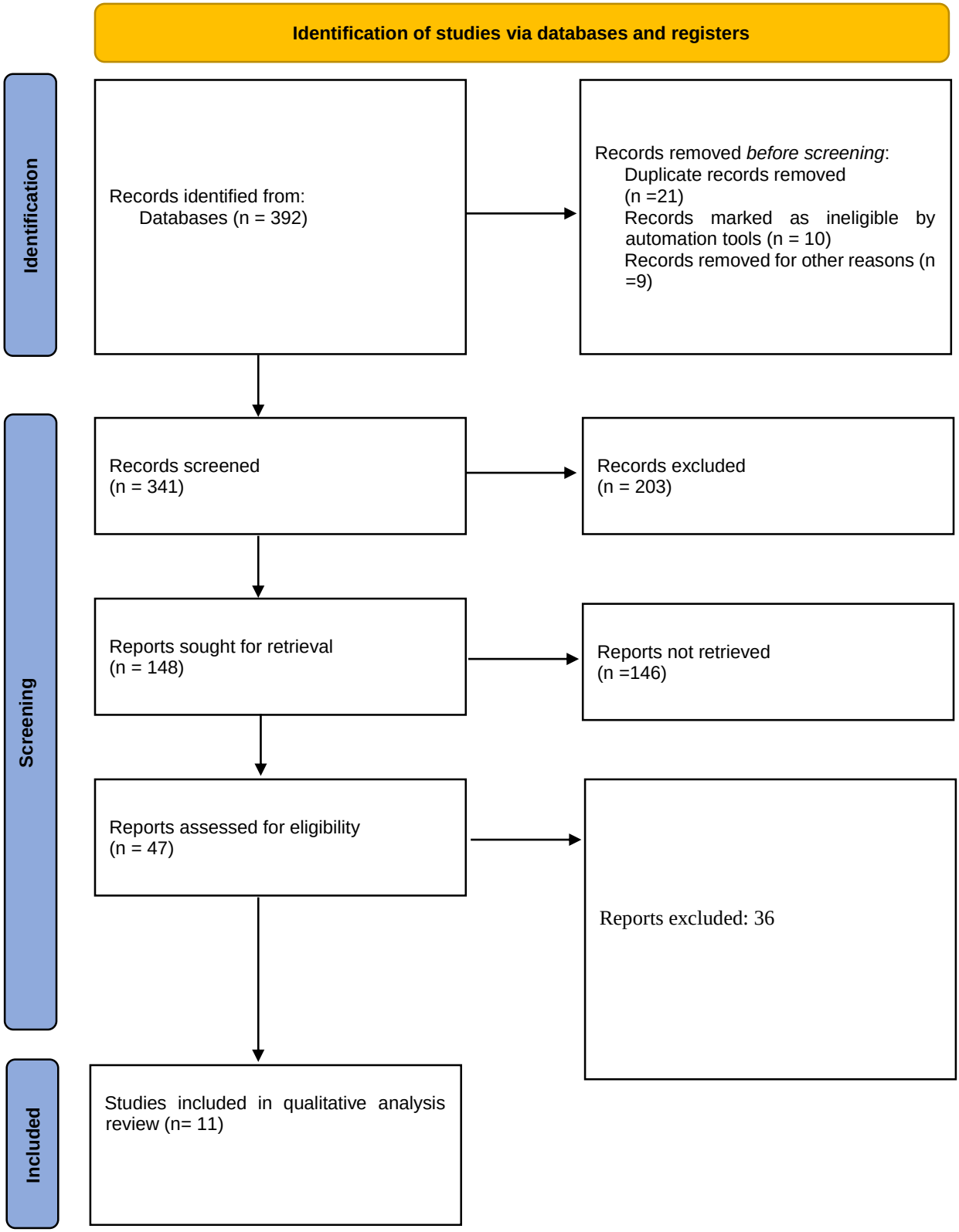


Figure 1: PRISMA flow chart

10/11/2026

Table 1. Primary studies contributing prevalence data

Study	Country and population	Diagnostic approach	PE, n/N (%)	Main interpretive limitation
Tillie-Leblond, 2006	France; prospective unexplained AECOPD	CTA and venous ultrasonography	49/197 (24.9)	Selected severe presentations (8)
Rutschmann, 2007	Switzerland; prospective emergency presentations	D-dimer, ultrasonography, CT	4/123 (3.3)	Four PE events (9)
Gunen, 2010	Turkey; prospective hospitalised AECOPD	CT angiography and ultrasonography	18/131 (13.7)	Single hospital population (10)
Choi, 2013	South Korea; prospective hospitalised AECOPD	CTPA and CT venography	5/103 (4.9)	Few events; imprecise predictors (11)
Akpinar, 2014	Turkey; prospective hospitalised AECOPD	CTPA and venous ultrasonography	50/172 (29.1)	Single hospital population (12)
Shapira-Rootman, 2015	Israel; prospective hospitalised AECOPD	D-dimer and CTPA evaluation	9/49 (18.4)	Small sample (13)
Chaudhary, 2021	India; prospective unexplained AECOPD	CTPA or venous imaging with clinical suspicion	14/100 (14.0)	One diagnosis without CTPA (14)
Couturaud, 2021	France; multicentre acute respiratory deterioration	Standardised algorithm within 48 hours	44/740 (5.9)	PE and VTE require separation (15)
Jiménez, 2021	Spain; randomised trial without initial PE suspicion	Active D-dimer and CTPA strategy	17/370 (4.6)	Intervention-arm diagnostic denominator (16)
Liu, 2023	China; prospective multicentre hospitalised AECOPD	CTPA and lower limb ultrasonography	266/1,580 (16.8)	Hospital population; broader VTE outcomes (17)
Rowe, 2026	Canada; retrospective multicentre emergency cohort	Routine selective investigation and administrative records	68/12,164 (0.56)	Incomplete investigation; ascertainment limitations (18)

Table 2. Reported associations with PE

Clinical feature	Reported association (95% CI)	Interpretation
Previous thromboembolism	RR 2.43 (1.49-3.94)	Association in unexplained exacerbations (8)
Malignancy	RR 1.82 (1.13-2.92)	Association within one cohort (8)
$PaCO_2$ reduction ≥5 mmHg	RR 2.10 (1.23-3.58)	Change from baseline (8)
Absent infectious symptoms	Adjusted OR 31 (2-563)	Marked imprecision (11)
D-dimer ≥500 µg/L	Adjusted OR 25 (1-464)	Marked imprecision; assay-specific threshold (11)
Obesity	Adjusted OR 4.97 (1.78-13.93)	Independent association in one cohort (12)
Lower limb asymmetry	Adjusted OR 2.33 (1.13-7.11)	Estimate from one cohort (12)
Respiratory rate ≥30/min	Adjusted OR 2.77 (1.08-6.71)	Secondary analysis of PEP/SLICE (19)
BNP concentration	Independent association; combined model AUC 0.64	Limited discrimination (19)

Discussion

The included studies indicate that PE accompanies a proportion of acute COPD presentations, although the size of that proportion depends strongly on recruitment criteria, investigation protocols, and the clinical setting in which patients are assessed at each participating center. The contrast between selected unexplained exacerbation cohorts and routine emergency presentations is therefore interpreted here as a difference in the populations and methods studied, rather than a direct measure

10/11/2026

of diagnostic performance across hospitals (8,14,18). In particular, the prevalence of embolism detected during systematic investigation does not establish the frequency of preventable missed diagnosis, since initial suspicion, diagnostic timing, and opportunities for recognition were not assessed consistently across the included clinical studies (9).

Reported predictors offer useful clinical context, with previous thromboembolism, malignancy, lower limb asymmetry, and respiratory findings identifying features associated with PE within particular study populations (8,12,14). A reduction in arterial carbon dioxide or respiratory alkalosis warrants interpretation against the patient's underlying respiratory physiology, since the original studies used different arterial carbon dioxide thresholds and did not establish a universal standalone diagnostic criterion (8,14). Wide confidence intervals in the Korean cohort limit the precision of estimates for individual features (11). The limited discrimination of the individual participant analysis and the need for prospective assessment of the COPD-specific strategy also indicate that associations measured within these cohorts do not constitute validated predictors of diagnostic error (19,20).

Evidence from general suspected-PE populations supports clinical probability assessment followed by an appropriate D-dimer strategy, with ADJUST-PE demonstrating the value of age-adjusted interpretation in selected patients with non-high clinical probability (22). The YEARS study similarly reduced imaging requirements through a structured combination of clinical features and differentiated D-dimer thresholds, with safety assessed through subsequent symptomatic thromboembolic events (23). Applying these findings to hospitalised COPD populations requires attention to the direct SLICE analysis, where adjusted thresholds increased false-negative classifications, indicating that diagnostic efficiency and diagnostic safety require separate assessment in this setting (21).

The SLICE trial does not establish a clinical benefit from routine active investigation in hospitalised exacerbations without initial PE suspicion, despite identifying additional emboli (16). Its confidence interval included benefit and harm for a composite of death, symptomatic thromboembolism, and COPD readmission, leaving uncertainty about individual outcomes (16). Likewise, higher mortality associated with thromboembolism in observational cohorts does not establish that universal imaging reduces mortality, because disease severity, comorbidity, and selection influence both thromboembolic risk and prognosis (10,17).

Several limitations affect interpretation, including differences in exacerbation definitions, small numbers of PE events in individual cohorts, variation in diagnostic verification, and exclusion of patients requiring particular forms of intensive respiratory support (8,9,11,14,16). Additional uncertainty arises when studies combine PE with deep venous thrombosis or analyse overlapping cohorts, making outcome separation and identification of repeated participants necessary for an accurate interpretation of the available evidence (17,19,20). Future studies require a clearly documented index assessment, independent adjudication of diagnostic delay, and follow-up that distinguishes previously present embolism from incident thrombosis, with reporting that preserves the difference between detecting additional disease and improving patient outcomes (7,9).

Conclusion

Pulmonary embolism is an established accompanying or alternative diagnosis in patients presenting with acute COPD exacerbations, with prevalence varying according to patient selection and diagnostic investigation. Previous thromboembolism, malignancy, lower limb asymmetry, absent infectious symptoms, and abnormal respiratory physiology were associated with PE in individual studies, although these findings

10/11/2026

did not establish predictors of preventable diagnostic error. The data supports explicit consideration of PE during the initial acute assessment and careful interpretation of clinical probability, biomarkers, and imaging, while the frequency of confirmed missed diagnosis remains uncertain because unsuspected embolism, delayed recognition, and newly developed thrombosis were not consistently separated.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AUC, area under the receiver operating characteristic curve; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CTA, computed tomography angiography; CTPA, computed tomography pulmonary angiography; DVT, deep venous thrombosis; OR, odds ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PE, pulmonary embolism; PEP, Prevalence of Symptomatic Pulmonary Embolism in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, risk ratio; SLICE, Significance of Pulmonary Embolism in COPD Exacerbations trial; VTE, venous thromboembolism.

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10/11/2026

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10/11/2026