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Original Article

Diagnostic Performance of the 4PEPS Score for Pulmonary Embolism in Hospitalized Patients with Acute Exacerbation of COPD

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ABSTRACT

Background: Pulmonary embolism (PE) can mimic acute exacerbations of chronic obstructive pulmonary disease (AECOPD), complicating diagnosis in hospitalized patients. The 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS) may facilitate clinical risk stratification and guide diagnostic investigations; however, its performance in this population requires further evaluation. **Aim of the study:** To evaluate the diagnostic performance of the 4PEPS score for detecting PE in hospitalized patients with AECOPD and compare its performance with D-dimer testing. **Methods & Materials:** This observational analytical study included 46 hospitalized patients with AECOPD at the National Institute of Diseases of Chest and Hospital, Dhaka, Bangladesh, from September 2022 to August 2023. Patients were selected using purposive sampling. Computed tomography pulmonary angiography (CTPA) served as the reference standard. The diagnostic performance of 4PEPS at a cutoff of ≥10 and D-dimer at a cutoff of ≥1.41 µg/dL was evaluated using sensitivity, specificity, area under the receiver operating characteristic curve (AUC), and additional diagnostic accuracy measures. **Result:** CTPA confirmed PE in 10 patients (21.74%). At the selected cutoff, 4PEPS demonstrated a sensitivity of 80.0%, specificity of 97.2%, and AUC of 0.899 (95% CI: 0.770–1.000). D-dimer demonstrated a sensitivity of 70.0%, specificity of 83.3%, and AUC of 0.797 (95% CI: 0.654–0.941). The 4PEPS score had a higher Youden index (0.772 vs 0.533), a higher diagnostic odds ratio (140 vs 11.67), and fewer misclassified patients (6.52% vs 19.57%) than D-dimer. The observed false-negative rates were 20.0% for 4PEPS and 30.0% for D-dimer. **Conclusion:** The 4PEPS score demonstrated better observed discriminatory performance than D-dimer for PE detection in hospitalized patients with AECOPD. Its high specificity and lower misclassification rate indicate potential clinical utility in guiding diagnostic evaluation. However, the small sample size and limited number of confirmed PE cases necessitate cautious interpretation and validation in larger, prospective, multicenter studies.

Keywords: *Acute exacerbation of COPD; pulmonary embolism; 4PEPS score; D-dimer; diagnostic accuracy.*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, progressive respiratory disorder characterized by persistent airflow limitation, chronic respiratory symptoms, and recurrent acute exacerbations [1]. Globally, COPD affected approximately 391.9 million people aged 30–79 years in 2019, corresponding to a prevalence of 10.3% in this age group [2]. Acute exacerbations of COPD (AECOPD) are associated with increased hospital admissions, prolonged hospitalization, and substantial morbidity and mortality. These episodes are commonly triggered by respiratory infections, environmental exposures, or other acute medical conditions [3]. However, pulmonary embolism (PE) may present with similar clinical features, including worsening dyspnea, tachycardia, hypoxemia, and chest discomfort, making its diagnosis particularly challenging in hospitalized patients with AECOPD [4]. Pulmonary embolism is a potentially life-threatening cardiovascular emergency that requires timely recognition and appropriate treatment [5]. Its clinical manifestations frequently overlap with those of acute COPD exacerbations, potentially resulting in delayed diagnosis or inappropriate treatment [6]. In patients with AECOPD, PE may be suspected when respiratory deterioration is disproportionate to the apparent exacerbation, when conventional treatment produces an inadequate response, or when additional clinical features suggest venous thromboembolism [1]. Although PE is not present in every patient admitted with AECOPD, overlooking this condition may lead to preventable complications and increased mortality. Therefore, identifying patients who require further diagnostic evaluation is an important component of hospital-based respiratory care [7]. The diagnosis of PE generally involves clinical probability assessment, D-dimer testing, and imaging investigations, particularly computed tomography pulmonary angiography (CTPA) [5]. D-dimer testing is useful for excluding PE in patients with an appropriately low or intermediate pretest probability when a validated threshold is applied [8]. However, D-dimer concentrations may increase during acute COPD exacerbations because of inflammation, infection, advanced age, and concurrent medical conditions [9]. Consequently, its specificity may be reduced in this population, leading to additional imaging, increased healthcare costs, and unnecessary exposure to contrast agents and radiation. Conversely, relying exclusively on clinical presentation may be insufficient because COPD-related symptoms can obscure the characteristic manifestations of PE [10]. The 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS) is a clinical decision tool developed to stratify patients according to their probability of PE and guide the selection of appropriate diagnostic investigations. By integrating clinical findings and relevant risk factors into a structured assessment, this approach aims to improve diagnostic efficiency and support the rational use of D-dimer testing and imaging. Its potential advantage lies in facilitating a probability-based diagnostic pathway rather than applying identical investigation strategies to all patients [11]. Nevertheless, the performance of clinical prediction tools may vary across patient populations, particularly among hospitalized individuals with acute

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respiratory illnesses and substantial comorbidity [12]. COPD-related symptoms, frequent comorbidities, and inflammatory changes may influence clinical probability assessment and the interpretation of diagnostic investigations [4]. Evidence regarding the performance of 4PEPS specifically in hospitalized patients with AECOPD remains an important consideration before its routine application in this setting. Assessing its diagnostic accuracy alongside established investigations, including D-dimer testing and appropriate reference-standard imaging, may help clarify its clinical usefulness. Therefore, this study aimed to evaluate the diagnostic performance of the 4PEPS score for detecting PE in hospitalized patients with AECOPD.

METHODS & MATERIALS

An observational analytical study was conducted among 46 hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) to evaluate the diagnostic performance of the 4PEPS score for pulmonary embolism (PE), using computed tomography pulmonary angiography (CTPA) as the reference standard. The study was carried out at National Institute of Diseases of Chest and Hospital, Mohakhali, Dhaka over the period from September 2022 to August 2023. Patients hospitalized with acute exacerbation of COPD who underwent clinical assessment and CTPA for suspected pulmonary embolism were included using a purposive sampling technique. The diagnostic accuracy of the 4PEPS score was assessed by comparing its classification with CTPA findings. The diagnostic performance of D-dimer was also evaluated for comparison.

Inclusion Criteria

- Hospitalized patients aged 18 years or older with acute exacerbation of COPD.
- Patients evaluated for suspected pulmonary embolism during hospitalization.
- Patients who underwent CTPA for confirmation or exclusion of pulmonary embolism.
- Patients with available clinical information required to calculate the 4PEPS score.
- Patients with available D-dimer results for comparative diagnostic analysis, where applicable.

Exclusion Criteria

- Patients without a confirmed clinical diagnosis of acute exacerbation of COPD.
- Patients without CTPA results.
- Patients with incomplete clinical records that prevented calculation of the 4PEPS score.
- Patients with missing D-dimer results, for analyses involving D-dimer.
- Patients with insufficient information to determine the final diagnostic classification.

Data Collection

Data were collected using a structured data collection form from clinical records, laboratory reports, and radiological findings. Sociodemographic information included age and gender. Clinical characteristics included documented comorbidities, particularly diabetes mellitus and hypertension. The 4PEPS score was calculated from the available clinical information, and patients were categorized according to the reported score groups of 0–5, 6–12, and ≥13. For diagnostic classification, a 4PEPS cutoff of ≥10 was used to define a positive test result.

CTPA findings were recorded as pulmonary embolism present or absent and were considered the reference standard for evaluating diagnostic performance. D-dimer levels were recorded, and a cutoff of ≥1.41 µg/dL was used for the comparative analysis, according to the supplied results. True-positive, true-negative, false-positive, and false-negative classifications were determined for both diagnostic tests. Sensitivity, specificity, area under the receiver operating characteristic curve (AUC), and 95% confidence intervals were assessed. Additional diagnostic measures included the Youden index, diagnostic odds ratio, false-positive rate, false-negative rate, and the proportion of misclassified patients.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized using mean and standard deviation or range, as appropriate. Diagnostic performance was evaluated by constructing contingency tables using CTPA as the reference standard. Sensitivity and specificity were calculated from the diagnostic classification counts. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory performance of the 4PEPS score and D-dimer, and the AUC with 95% confidence intervals was reported. The Youden index, diagnostic odds ratio, false-positive rate, false-negative rate, and overall misclassification rate were calculated where applicable. A p-value of less than 0.05 was considered statistically significant for relevant comparisons.

RESULT

Among the 46 hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), the largest proportion were aged >64 years (41.30%), followed by those aged 50–64 years (32.61%) and <50 years (26.09%). The reported mean age was 58.2±9.2 years. Diabetes mellitus was present in 32.61% of patients, while hypertension was reported in 30.43%. No documented comorbidity was observed in 36.96% of patients (*Table I*).

Table I
Age Distribution and Comorbidities of Patients with Acute Exacerbation of COPD (*n*=46).

Variables	Frequency (n)	Percentage (%)
Age (years)		
<50	12	26.09
50-64	15	32.61
>64	19	41.30
Mean ±SD	58.2±9.2	
Range (min-max)	40-73	
Comorbidities		
Diabetes mellitus	15	32.61
Hypertension	14	30.43
No documented comorbidity	17	36.96
Total	46	100.00

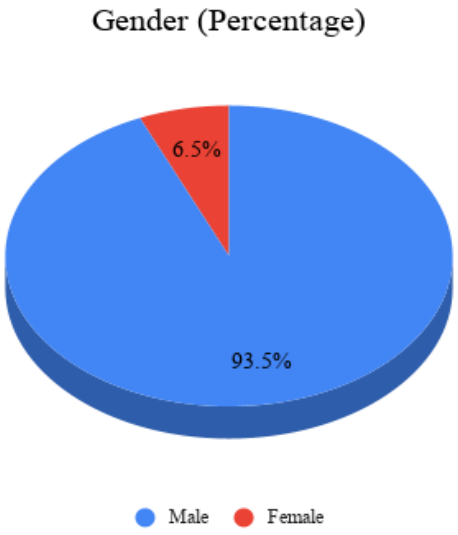

Figure 1: Distribution of Patients by Gender (*n*=46).

93.5% patients were male (**Figure 1**). CT pulmonary angiography (CTPA) confirmed pulmonary embolism (PE) in 10 patients (21.74%), whereas 36 patients (78.26%) had no evidence of PE. Regarding 4PEPS score categories, 35 patients (76.09%) scored 0–5, five (10.87%) scored 6–12, and six (13.04%) had scores ≥13 (*Table II*).

Table II
Prevalence of CTPA-confirmed pulmonary embolism and distribution of 4PEPS scores.

Characteristic	Frequency (n)	Percentage (%)
CTPA findings		
Pulmonary embolism present	10	21.74
Pulmonary embolism absent	36	78.26
4PEPS score category		
0–5	35	76.09
6–12	5	10.87
≥13	6	13.04
Total	46	100.00

Using a 4PEPS score cutoff of ≥10, 9 patients (19.57%) were classified as test-positive. Of these, 8 (80.00%) were CTPA-positive and 1 (2.78%) was CTPA-negative (*Table III*).

Table III
Diagnostic classification by 4PEPS at the cutoff of ≥10 against CTPA.

4PEPS classification	CTPA-positive, n (%)	CTPA-negative, n (%)	Total, n (%)
Score ≥10 (test positive)	8 (80.00)	1 (2.78)	9 (19.57)

Receiver operating characteristic analysis demonstrated better diagnostic performance for 4PEPS than for D-dimer. The 4PEPS score had a sensitivity of 80.0%, specificity of 97.2%, and area under the curve (AUC) of 0.899 (95% CI 0.770–1.000) at a cutoff of ≥10.0. In comparison, D-dimer at a cutoff of ≥1.41 µg/dL had a sensitivity of 70.0%, specificity of 83.3%, and AUC of 0.797 (95% CI 0.654–0.941) (*Table IV*).

Table IV
Receiver operating characteristic analysis of 4PEPS and D-dimer.

Diagnostic test	Selected cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI for AUC
4PEPS	≥10.0	80	97.2	0.899	0.770–1.000
D-dimer	≥1.41 µg/dL	70	83.3	0.797	0.654–0.941

The comparative diagnostic measures further favored 4PEPS, with a Youden index of 0.772 and diagnostic odds ratio of 140, compared with 0.533 and 11.67 for D-dimer, respectively. The false-positive and false-negative rates were 2.78% and 20.0% for 4PEPS, compared with 16.67% and 30.0% for D-dimer. Overall, 4PEPS misclassified three patients (6.52%), whereas D-dimer misclassified nine (19.57%) (*Table V*).

Table V
Additional comparative measures derived from the diagnostic classification counts.

Measure	4PEPS	D-dimer
Youden index	0.772	0.533
Diagnostic odds ratio	140	11.67
False-positive rate (%)	2.78	16.67
False-negative rate (%)	20	30
Misclassified patients, n (%)	3 (6.52)	9 (19.57)

The 4PEPS score correctly identified 8 patients (17.39%) with pulmonary embolism as true positives and 35 (76.09%) without pulmonary embolism as true negatives. It produced 1 false-positive result (2.17%) and 2 false-negative results (4.35%). In comparison, D-dimer correctly classified 7 patients (15.22%) as true positives and 30 (65.22%) as true negatives, while 6 (13.04%) were false positives and 3 (6.52%) were false negatives (*Table VI*).

Table VI
Distribution of correct and incorrect diagnostic classifications.

Classification outcome	4PEPS, n (%) of all patients	D-dimer, n (%) of all patients
True positive	8 (17.39)	7 (15.22)
True negative	35 (76.09)	30 (65.22)
False positive	1 (2.17)	6 (13.04)
False negative	2 (4.35)	3 (6.52)
Total	46 (100.00)	46 (100.00)

DISCUSSION

The diagnostic performance of the 4PEPS score demonstrated favorable discrimination for pulmonary embolism (PE) among hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). In the present study, PE was confirmed by computed tomography pulmonary angiography (CTPA) in 10 of 46 patients (21.74%). At a cutoff of ≥10, 4PEPS achieved 80.0% sensitivity, 97.2% specificity, and an area under the receiver operating characteristic curve (AUC) of 0.899 (95% CI: 0.770–1.000). In comparison, D-dimer demonstrated 70.0% sensitivity, 83.3% specificity, and an AUC of 0.797 (95% CI: 0.654–0.941). Roy et al. reported AUC values of approximately 0.78–0.79 in external validation cohorts, whereas Stals et al. reported an AUC of 0.82 (95% CI: 0.80–0.84) [11, 13]. Although the AUC in the present study was higher, the small sample size and wide confidence interval limit direct comparisons. The mean age was 58.2±9.2 years, and 41.30% of patients were older than 64 years. Diabetes mellitus and hypertension were present in 32.61% and 30.43%, respectively, while 36.96% had no documented comorbidity. Previous research has highlighted the diagnostic challenges associated with PE during COPD exacerbations because respiratory symptoms may overlap. The COPD-specific analysis of the PEP trial also emphasized the importance of evaluating PE in this population [14]. However, the present study did not establish associations between age, comorbidities, and PE occurrence; these findings therefore provide descriptive clinical context rather than evidence of independent risk factors. The 4PEPS score distribution showed that 76.09% of patients scored 0–5, 10.87% scored 6–12, and 13.04% scored ≥13. The observed PE prevalence of 21.74% was higher than the approximately 11–17% reported in some previous COPD exacerbation studies, although prevalence varies with patient selection and diagnostic procedures [14]. The difference may reflect the selection of hospitalized patients who underwent CTPA rather than an unselected COPD population. Importantly, a low score category alone does not establish that PE can be safely excluded; the validated 4PEPS diagnostic algorithm incorporates clinical probability, appropriate D-dimer thresholds, and imaging decisions. At the selected cutoff, 4PEPS correctly identified eight of ten PE cases and 35 of 36 patients without PE, resulting in two false-negative and one false-positive classifications. D-dimer correctly identified seven PE cases and 30 patients without PE, with three false-negative and six false-positive classifications. These findings indicate fewer false-positive classifications with 4PEPS in the present sample. However, the missed PE cases remain clinically important, and the limited number of confirmed cases reduces the precision of sensitivity estimates. Previous validation studies by Roy et al. and Stals et al. support the potential usefulness of 4PEPS as a structured diagnostic strategy, although their larger populations and algorithm-based assessments differ from the selected cutoff evaluated here [11,13]. The receiver operating characteristic analysis further favored 4PEPS, with an AUC of 0.899 compared with 0.797 for D-dimer. The AUC reported by Chiang et al. was 0.85 (95% CI: 0.82–0.88), also lower than the point estimate in the present study [15]. Nevertheless, the wide confidence interval in the current analysis indicates uncertainty, and no formal statistical comparison of the AUCs was provided. The Youden index was higher for 4PEPS than D-dimer (0.772 versus 0.533), while the diagnostic odds ratio was 140 versus 11.67. Overall, 4PEPS misclassified 3 patients (6.52%), compared with 9 (19.57%) for D-dimer. These results suggest better observed classification performance, but differences in thresholds and study populations limit comparisons with previous investigations. The findings have potential clinical relevance because a structured diagnostic approach may help guide further investigation and reduce unnecessary imaging. However, the PEP trial analysis demonstrated that imaging-sparing strategies in COPD exacerbations may involve a trade-off between reduced CTPA use and increased diagnostic failure [14]. The present study did not evaluate actual imaging reduction or subsequent clinical outcomes. Its principal limitations were the small sample, only ten confirmed PE cases, uncertainty around diagnostic estimates, and evaluation of a selected cutoff rather than the complete 4PEPS algorithm. Overall, 4PEPS showed better observed diagnostic discrimination than D-dimer in this sample, supporting further prospective validation before routine implementation in hospitalized patients with acute exacerbation of COPD.

LIMITATION

This study had several limitations. First, the relatively small sample size of 46 patients, including only 10 CTPA-confirmed pulmonary embolism cases, may have reduced the precision and generalizability of diagnostic accuracy estimates. Second, the single-center design and purposive sampling may have introduced selection bias. Third, inclusion was restricted to hospitalized patients with acute exacerbation of COPD who underwent CTPA for suspected pulmonary embolism, potentially limiting applicability to other clinical settings. Finally, the selected

diagnostic cutoffs may influence performance estimates, and external validation was not performed.

CONCLUSION

The 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS) demonstrated promising diagnostic performance for pulmonary embolism among hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. At the selected cutoff of ≥10, the score achieved a sensitivity of 80.0%, specificity of 97.2%, and an area under the receiver operating characteristic curve (AUC) of 0.899, outperforming D-dimer in the observed sample. The 4PEPS score also demonstrated fewer false-positive results and a lower overall misclassification rate. These findings indicate its potential value in supporting clinical risk stratification and guiding further diagnostic investigations. However, the small sample size and limited number of confirmed cases warrant cautious interpretation and larger prospective validation before routine clinical implementation.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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