D-dimer value for predicting pulmonary embolism in COVID-19 patients: A retrospective study

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ABSTRACT

Introduction: Pulmonary embolism (PE) is a significant complication in patients with COVID-19, often associated with elevated D-dimer levels. However, there remains uncertainty around the D-dimer threshold for predicting PE in COVID-19 patients as it is influenced by multiple disease factors. This study aimed to establish the D-dimer cut-off value for predicting pulmonary embolism (PE) in patients with COVID-19, evaluate the sensitivity and specificity of this cut-off value, and describe the occurrence of PE and its significant factors.

Materials and Methods: A retrospective analysis was conducted on 320 patients with COVID-19 who underwent computed tomography pulmonary angiography (CTPA) due to clinical suspicion of PE between 2020 and 2021 at a single centre in Malaysia. Clinical and biological factors associated with PE were analyzed, including age, sex, race, and D-dimer levels.

Results: Among the study population, 23.4% of males and 15.4% of females tested positive for PE, with no significant differences noted across racial groups. Age was significantly associated with PE development (p = 0.013). D-dimer levels in PE-positive patients were five times higher than in PE-negative patients (p = 0.001). An optimal D-dimer cut-off of 2799 ng/ml level was identified with an area under the curve (AUC) of 0.744 (95% CI: 0.676–0.813), and sensitivity of 81%, and specificity of 51%.

Conclusion: This study highlights the role of D-dimer as a predictive biomarker for PE in COVID-19 patients. The identified cut-off value offers a practical threshold for clinical decision-making, balancing sensitivity and specificity. Further studies are needed to validate these findings in broader population.

KEYWORDS:
Computed Tomography Pulmonary Angiogram (CTPA), Pulmonary Embolism (PE), D-Dimer, COVID-19

INTRODUCTION

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), posed a significant public health challenge. This was particularly due to its link with thromboembolic and hypercoagulable events, such as pulmonary embolism (PE). COVID-19 infection triggers a complicated state of increased clotting and inflammation, which results in elevated levels of D-dimer. These D-dimer levels serve as biomarkers to assess the risk of developing PE. Recent studies have highlighted the critical role of D-dimer levels in predicting PE in COVID-19 patients, a D-dimer cut-off of 2903 ng/mL demonstrated an 81% sensitivity for predicting PE in COVID-19 patients undergoing computed tomography pulmonary angiography (CTPA).[1] Another study also recommended that higher D-dimer cut-off value, such as 2000–5000 ng/mL, can highly predict PE while minimizing unnecessary CTPA.[2] Furthermore, in the emergency department unit, thresholds as low as 1815 ng/mL represent 93% sensitivity of PE.[3]

The associated coagulopathy nature of COVID-19 and the various presentations of PE in different patient populations underscore the need to understand the D-dimer cut-off value. This value and characterization of PE such as the location will be helpful for clinicians to determine the likelihood of PE and the next steps in management. Peripheral PE locations are more common in COVID-19 patients, which may highlight a localized thrombotic process differences from traditional embolic pathways.[4]

This study aimed to determine the optimal D-dimer cut-off value for predicting PE in hospitalized COVID-19 patients and to evaluate its diagnostic performance in terms of sensitivity and specificity. Additionally, the study sought to explore demographic and clinical factors associated with the occurrence of PE. Given the burden of COVID-19 and its evolving clinical presentations, understanding the predictive value of D-dimer levels remains challenging for improving diagnostic strategies and minimizing resource overuse.

MATERIALS AND METHODS

Study Design and Participants

A retrospective analysis was conducted on 320 patients at Hospital Sultanah Nur Zahirah in Kuala Terengganu, Malaysia, during January 2020 and December 2021. The inclusion criteria included those who confirmed COVID-19 diagnosis with clinical suspicion of PE and underwent CTPA. The exclusion criteria are incomplete CTPA or missing D-dimer data. The clinical suspicion is based on clinical

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Table I: Location of pulmonary embolism (PE) in the CTPA

Location of PE		N (%)
Laterality	Unilateral	46 (73)
	Bilateral	17 (26.9)
Affected artery	Pulmonary artery trunk	1(1.6)
	Main pulmonary arteries	10 (15.9)
	Lobar pulmonary arteries	16 (25.4)
	Segmental pulmonary arteries	25 (39.7)
	Subsegmental pulmonary arteries	3 (4.8)
Location	Right upper lobe	16 (26.7)
	Right lower lobe	20 (33.3)
	Middle lobe	4 (6.7)
	Left upper lobe	7 (11.7)
	Left lower lobe	13 (21.7)

Table II: PE comparison among COVID-19 patients

Variable	PE-positive (63)	PE-negative (257)	p value
Mean age (SD) years	59.89 (13.61)	54.91 (15.93)	0.013 [a]
Gender			
Male	40 (23.4%)	131 (76.6%)	0.074 [b]
Female	23 (15.4%)	126 (84.6%)	
Race			
Malay	61 (19.2%)	256 (80.8%)	0.100 [c]
Chinese	2 (66.7%)	1 (33.3%)	
D-dimer (Median (IQR))	17000 (28801)	3073 (5249)	<0.001 [d]

[a] Independent t-test, [b] Pearson chi-square test, [c] Fisher's exact test, [d] Mann Whitney test

symptoms of dyspnoea, chest pain, hypoxia and elevated D-dimer.

The approval for the research was obtained from the Research Ethics Committee of the Ministry of Health Malaysia (NMRR ID-23-01789-5R6). The requirement for informed consent was waived, given the retrospective nature of the analysis. All collected data were fully anonymized to maintain confidentiality and prevent any potential identification of the patients.

To ensure a standardized and secure method of data collection, allowing for comprehensive analysis while upholding ethical research standards, patient imaging and associated clinical information were systematically retrieved from the hospital picture archiving and communication system.

CTPA image acquisition

A 640-multislice CT scan (Aquilion One, Canon Medical Systems LTD) was used for the CTPA assessment. For the image aquisition, the entire thorax was scanned in a craniocaudal direction from the top of the lung to the bottom of the diaphragm. To reduce breathing artefact, all patients were instructed to temporarily hold their breath during the scanning. The pulmonary trunk was used as the region of interest for an automatic bolus-tracking approach, with a threshold of 100HU and a fixed latency of 5 s before picture capture. A single breath-hold was used to acquire CTPA pictures.

Image interpretation

The location of the pulmonary thrombus was identified for each patient. Information which was recorded includes the laterality (unilateral or bilateral), the affected pulmonary artery (trunk, main, lobar, segmental, or subsegmental) and the affected lobe (right upper lobe, right lower lobe, middle lobe, left upper lobe or left lower lobe).

Statistical analysis

The interquartile range (IQR) was used to depict the median of continuous variables. Numbers and percentages were used to describe categorical variables. Fisher's exact test, Pearson chi-square test, Mann-Whitney test, and Independent t-test were all used to evaluate patient characteristics between the PE-positive and PE-negative groups.

The optimal D-dimer cutoff point for PE was determined based on Receiver operating characteristic (ROC) analysis and area under the curve (AUC). The p-value was considered statistically significant of less than 0.05. Statistical analyses were done using SPSS 21.0 software.

RESULTS

PE Imaging findings

A total of 320 patients were included in this study. There were 63 patients (19.7%) who were diagnosed with PE while the remaining were negative for PE. Unilateral PE was 3-fold higher than bilateral involvement. The right lower lobe was the commonest affected site. The distribution of the affected arteries were shown in Table I

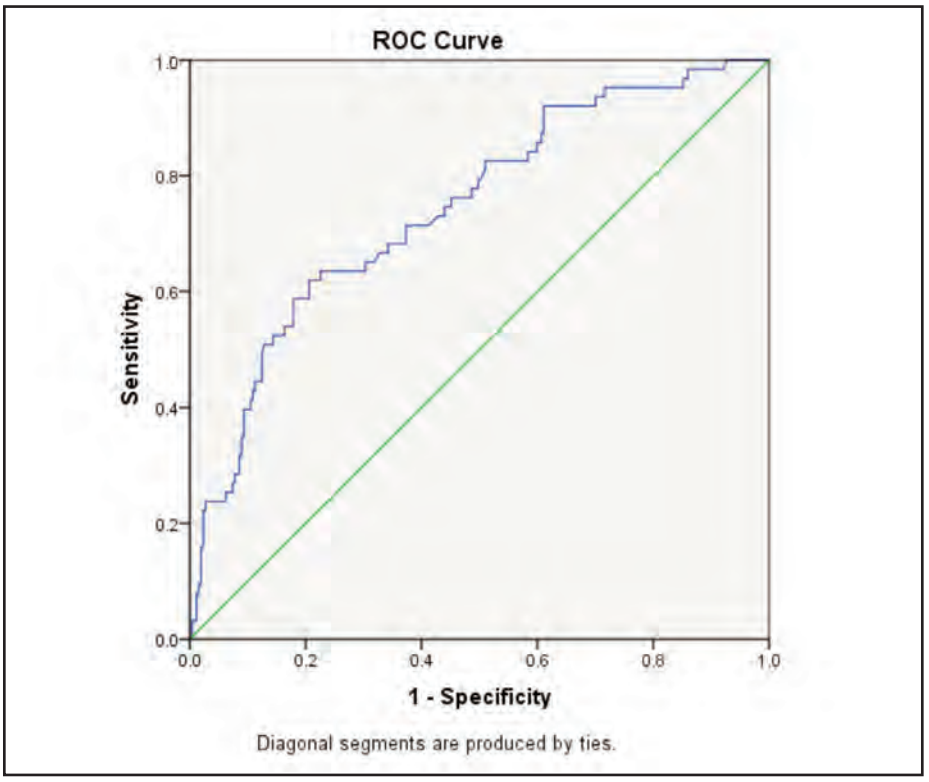

Fig. 1: ROC curve for specificity and sensitivity based on D-dimer value

Comparison of Pulmonary Embolism (PE) among COVID-19 Patients

The mean age was higher among patients diagnosed with PE compared to PE-negative patients and it was statistically significant (p=0.013). There was a higher percentage of males than females diagnosed with PE. However, this difference was not statistically significant (p=0.074). The demographic data was shown in Table II.

The D-dimer values were almost five times higher in PE-positive patients, with a median of 17,000 ng/mL (IQR: 28,801), than in PE-negative patients (3,073 ng/mL; IQR: 5,249) (p<0.001) as shown in the Table II.

ROC Analysis for D-dimer Cutoff

The ROC curve analysis for D-dimer values indicated an optimal cut-off value of 2,799 ng/mL, achieving an Area Under the Curve (AUC) of 0.744 (95% CI: 0.676–0.813). At this cut-off value for predicting PE, the D-dimer demonstrated a sensitivity of 81% and a specificity of 51% (Figure 1).

DISCUSSION

D-dimer level is crucial in predicting PE in COVID-19 patients. D-dimer with a cut-off value of 2799 ng/mL, can be used to predict the presence of PE in patients with COVID-19. This finding was consistent with other studies, include a multi-centre study with the D-dimer cut-off value of 2494 ng/mL, while other studies reported a cut-off value of between 2600 - 2903 ng/mL.[1,5-6] Those findings highlighted the value of D-dimer as biomarker for diagnosing PE among COVID-19 patients. However, there was a study with a lower D-dimer cut-off value of 1815 ng/mL, with sensitivity of 93% for diagnosis of PE.[3]

A clinical scoring system with the integration of biomarkers with the Wells or Geneva criteria was used in diagnosing PE among patients with COVID-19 in few studies. Those studies have demonstrated that the clinical scoring system enhanced diagnostic precision without requiring a CTPA, mostly in older populations.[7] An elevated D-dimer level is also present in other diseases such as malignancy, sepsis, and autoimmune disorders.

While the D-dimer cut-off value may be useful in predicting the presence of PE, it can be used to avoid unnecessary CTPA. An adjusted D-dimer cut-off value of 2000 ng/mL was found to have a high negative predictive value for critically ill patients to be diagnosed with PE in a study, hence avoiding any unnecessary imaging.[8]

This study also suggested the need to treat a high-risk patient for PE earlier with an anticoagulation. A study has showed that in high risk patients with PE, the PE risk increased to four-fold in the absence of anticoagulation.[9] Other studies have also found that patients on therapeutic-dose anticoagulation prior to hospitalization or who have received prophylactic-dose anticoagulation during their hospital stay had reduced incidences of pulmonary embolism.[10]

Another important finding of this study was the incidence of PE in segmental arteries, with right-sided and unilateral involvement being the most prevalent. These findings were consistent with previous worldwide studies pointing to

morphological and hemodynamic predispositions in PE linked to COVID-19.[11-13] Further studies may be required to study localized thrombosis processes, which diverge from conventional embolic pathways. There was emerging evidence of microangiopathy involving small vessels, mainly in peripheral and unilateral PE among patients with COVID-19. We was not able to study such changes due to the limited information of the macrovascular findings with a standard CTPA.

Microvascular diseases such as microangiopathy, which are often associated with microembolism, cannot be accurately evaluated by using a conventional computed tomography (CT) imaging. Future studies incorporating dual-energy CT and perfusion imaging could give further insight into these changes in small vessels and their clinical impact.[11-13]

The findings in this study reinforce the utility of D-dimer as a critical biomarker across various thrombotic illnesses, including COVID-19. The integration of clinical probability models with biomarkers serves as a framework for more efficient diagnostic strategies.

LIMITATION

Limitations in this retrospective study include a single-centre study design and absence of information related to the co-morbidities. Further studies are required to identify age-adjusted and population-specific D-dimer cut-off values in high risk patients especially among patients with COVID-19.

CONCLUSION

This study suggested that the D-dimer value can be used as a predictive biomarker of diagnosis of PE in COVID-19 patients. This biomarker can be used particularly in the determining the need for pulmonary imaging and the initiation of anticoagulation. Future multi-centre studies should be carried out with broader datasets to validate these conclusions and investigate the impact of comorbid conditions on the D-dimer cut-off values.

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