ORIGINAL ARTICLE

Deciphering the Coagulation Factors in Pulmonary Embolism Incident-Based Thorax Enhanced Chest CT in COVID-19 Patient

Wan Betty Pratiwi[1], Noni Novisari Soeroso[1*], Setia Putra Tarigan[1], Muntasir Abdullah[1], Rosita Juwita Sembiring[2,3], Azizah Ghanie Icksan[4], Netty Delvrita Lubis[5], Putri Chairani Eyanoer[6]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[3]Philosophy Doctor in Medicine Program, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[4]Department of Radiology, Persahabatan National Respiratory Referral Hospital, Universitas Pembangunan Nasional, Jakarta, Indonesia.
[4]Department of Radiology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[5]Department of Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

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ABSTRACT

Introduction: Pulmonary embolism is associated with coagulopathy in COVID-19. It is one of the causes of death in COVID-19 cases and is often underdiagnosed in Indonesia because computed tomography-pulmonary angiography (CTPA) is not used as the gold standard. This study aimed to find an association between coagulation factors and the risk of pulmonary embolism based on the thorax CT scan of moderate to severe COVID-19 patients and to evaluate the effectiveness of thorax CT scan results with IV contrast in diagnostic settings rather than gold standard CTPA.

Methods: This study used a prospective analytical design with a cross-sectional approach. The study participants were 45 COVID-19 patients admitted to Santa Elisabeth Hospital, Medan, from November 2020 until November 2021. Patients were identified with moderate to severe degrees of COVID-19 and elevated D-dimer and subsequently instructed to undergo a thorax CT scan with IV contrast. The data was analyzed using dependent t-test statistical analysis. The p-value < 0.05 was noted as significant.

Results: Moderate to severe coagulation factor values in COVID-19 patients with mean + SD PT, APTT, D-dimer, fibrinogen, and platelets were 14.11; 30.65; 1172.14; 423.56, and 215.822, respectively. In this study, 22 (48.9%) patients experienced a pulmonary embolism, while the other 23 (51.1%) did not. No significant correlation was found between all coagulation factors and embolism (p > 0.05). The mean + SD well score for pulmonary embolism was 0.23 + 0.57.

Conclusion: Pulmonary embolism was detected in 22 patients (48.49%) with moderate to severe COVID-19 who developed hypercoagulation as indicated by the thorax CT scan with IV contrast. This case was quite common. In resource-constrained situations, a thorax CT scan with IV contrast may replace CTPA in diagnosing/detecting the presence of pulmonary embolism.

INTRODUCTION

Patients with severe/acute COVID-19 may present with acute respiratory distress syndrome and metabolic acidosis.[1] One of the key features of a poor prognosis is coagulopathy. Coagulopathy is an important and persistent phenomenon associated with negative results in patients with sepsis due to various infectious pathogens. Respiratory symptoms are predominant, but recent evidence has shown that patients with severe COVID-19 often develop coagulation disorder (coagulopathy).[2]

A pulmonary embolism is a disruption to the flow of blood in the pulmonary artery or its branches by a thrombus originating somewhere else. In deep vein thrombosis (DVT), a thrombus develops within the deep veins, most commonly in the lower extremities.[3] Additional imaging techniques can be used to determine

*Corresponding author: noni@usu.ac.id

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the presence of pulmonary embolism and its severity. Imaging techniques for enhancing pulmonary embolism diagnosis is still debatable. Although a chest X-ray cannot rule out pulmonary embolism, it is necessary to direct further tests and identify another diagnosis. Pulmonary multi-detector computed tomography (CT) angiography is the gold standard to diagnose pulmonary embolism.[4]

The complete coagulation parameters have prognostic value and are important therapeutic targets for patients with moderate to severe COVID-19. These coagulation parameters include activated partial thromboplastin time (APTT), D-dimer, platelets, prothrombin time, antithrombin activity (AT), fibrinogen degradation products (FDP), and fibrinogen. Elevated D-dimer and FDP levels, prolonged prothrombin time (PT), and activated partial thromboplastin time (APTT) were 71.4% of non-COVID-19 survivors compared to COVID-19 survivors on admission (if p-value < 0.05, it will be noted as significant).[2]

This coagulopathy is associated with pulmonary embolism and deep vein thrombosis (DVT). COVID-19 survivors with pulmonary embolism have higher D-dimer levels than patients with only pulmonary embolism. In COVID-19 survivors, D-dimer values >2660 μg/L had a 100% sensitivity (95%CI 88-100) and 67% sensitivity (95%CI 52-79) for pulmonary embolism according to CT angiography image.[5] A complete post-mortem full-body examination revealed a large thrombus that occludes the main pulmonary artery as the risk factor of death.[6]

A commonly used diagnostic imaging method for pulmonary embolism is computed tomography-pulmonary angiography (CTPA).[1] However, due to the limited number of CTPA facilities in Indonesia, pulmonary embolism is underdiagnosed. This study aimed to find an association between coagulation factors and the risk of pulmonary embolism based on the thorax CT scan of moderate to severe COVID-19 patients and to evaluate the effectiveness of thorax CT scan results with IV contrast in diagnostic settings rather than gold standard CTPA.

METHODS

Study Design

This was a prospective analytical study with a cross-sectional approach conducted at Santa Elisabeth Hospital, Medan, from November 2020 until November 2021.

Samples and Patients

Sample selection was performed using a consecutive sampling method, and 45 patients were selected. Patients who were COVID-19 positive with a moderate-to-severe degree of severity, hypercoagulation, and aged >18 years old were included as participants. Patients who fulfilled the inclusion criteria had a thorax CT scan with IV contrast performed using the injector. Those with unstable or untransportable conditions and contraindications for the IV contrast thorax CT scan were excluded. All subjects underwent an IV contrast thorax CT scan during hospital treatment.

Thorax CT Scan with IV Contrast Examination

The thorax CT scan procedure was performed for the patients diagnosed with COVID-19 and fulfilled the inclusion and exclusion criteria during their stay in Santa Elisabeth Hospital, Medan. The thorax CT scan was performed upon the patient's presence using GE Brightspeed 8 Slice CT scan machine. The patient lied on the scanning table and was instructed to breathe in and hold. The scan parameters were as follows: scan direction (Caudrocranial), tube voltage (120Kv), tube current (2 Fs), dose modulation (Smart Dose), slice collimation (8x1.25mm), total exposure time (18.38 seconds).

Analysis of the IV Contrast Thorax CT Scan Image

A radiologist evaluated each patient's CT image to detect the presence of occlusion in the pulmonary artery and to locate the location of the occlusion, if any. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS). Univariate analysis was used to present the frequency and percentage of non-parametric variables, while mean ± standard deviation for non-parametric variables. Bivariate analysis was performed using the chi-square test or Fisher exact, where p-value < 0.05 was significant.

Clinical Spectrum of COVID-19 Infection

- Asymptomatic: Individuals who test positive for SARS-CoV-2 using a virologic test (PCR test or an antigen test) but do not exhibit symptoms typical with COVID-19.
- Mild illness: if they exhibit any of COVID-19 signs and symptoms (including cough, fever, sore throat, headache, malaise, muscular pain, nausea, diarrhea, vomiting, and a loss of taste and smell), but not abnormal chest imaging, dyspnea, or shortness of breath.

- Moderate illness: those who exhibit signs of lower respiratory disease on clinical examination or imaging and have an oxygen saturation level of less than 94%, as determined by pulse oximetry (SpO_2).
- Severe illness: patients with SpO_2 below 94%, a PaO_2/FiO_2 ratio below 300 mmHg, a respiratory rate above 30 breaths per minute, or lung infiltrates above 50%.
- Critical illness: people with multiple organ dysfunction, septic shock, and/or respiratory failure are said to have an acute disease.

Laboratory Value as a Predictor of COVID-19-Associated Coagulopathy (CAC)

This study analyzed some laboratory values as a predictor of COVID-19-associated coagulopathy (CAC). Numerous laboratory results have been shown to correlate with disease severity and to be representative of the hypercoagulable condition present in the majority of critically ill COVID-19 patients. One of these is an increase in D-dimer levels, which are indicators of both clotting and fibrinolysis, a decrease in procoagulant proteins like factor V, factor VIII, and fibrinogen, and an increase in inflammatory markers like 1-acid glycoprotein, C-reactive protein (CRP), ferritin, procalcitonin, and high-sensitivity troponin (acute phase reactants).[7–10]

Ethical Clearance

This study had been approved by the Ethical Clearance Committee of the Faculty of Medicine, Universitas Sumatra Utara, with the registered number 654/KEP/USU/2021.

RESULTS

This study involved 45 samples, of which 29 (64.4%) were males, and 16 (35.6%) were females (Table 1). The average age of the subjects was 52.1 ± 11.5 years old. They were COVID-19 patients who displayed the following symptoms: fever (42 people, 93.3%), cough (40, 88.9%), and breathing problems/chest pain (29, 64.4%). Table 1 shows that subjects generally did not have anosmia (29, 64.4%), ageusia (34, 73.3%), nausea (23, 51.2%), vomiting (31, 68.9%), and diarrhea (34, 75.6%). In general, the study subjects' comorbidities were diabetes mellitus (35.7%), hypertension (30.9%), and congestive heart failure (CHF) (19%) (Table 1).

Table 1. Characteristics, symptoms, and degree of study samples (n = 45)

	n	%	Mean	SD
Age			52.1	11.5
Sex				
Male	29	64.4		
Female	16	35.6		
Symptoms				
Fever	42	93.3		
Cough	40	88.9		
Chest pain	29	64.4		
Anosmia	16	35.6		
Ageusia	11	24.4		
Nausea	22	48.8		
Vomit	14	31.1		
Diarrhea	11	24.4		
Comorbid				
Malignancy	2	4.7		
Diabetes mellitus	15	35.7		
Hypertension	13	30.9		
Congestive heart failure	8	19.0		
Asthma	2	4.7		
Tuberculosis	2	4.7		

The values of coagulation factors found in moderate-severe COVID-19 patients in this study were mean ± SD PT 14.11 ± 1.82, APTT 30.65 ± 7.70, D-dimer 1172.14 ± 838.95, fibrinogen 423.56 ± 88.91, and thrombocyte 215.822 ± 74.676, respectively. Delta for PT and APTT levels with control were -0.21 and 0.49 seconds, where PT and APTT levels were normal (Table 2).

Table 2. Characteristics of the levels of coagulation factors in the moderate-severe COVID-19 patients

Coagulation Factors	Moderate to Severe COVID-19 Patients		
	Mean ± SD	Min - Max	Delta
PT	14.11 ± 1.82	11.2 – 20.1	-0.21
APTT	30.65 ± 7.70	17.70 – 56.40	0.49
D-dimer	1172.14 ± 838.95	513.0 – 3696.7	
Fibrinogen	423.56 ± 88.91	239.0 – 609.0	
Thrombocyte	215,822 ± 74,676	98,000-329,000	

Pulmonary embolism occurred in 22 patients (48.9%) of 45 severe-moderate COVID-19 patients in this study. Twenty-three patients (51.1%) did not develop pulmonary embolism. Based on the location, the number of lung embolisms found in lobar, segmental, lobar and segmental was 14 (63.6%), 3 (13.6%), and 5 (22.7%), respectively (Table 3).

Table 3. Characteristics and the number of occurrences of pulmonary embolisms in moderate to severe COVID-19 patients

Pulmonary Embolism	n	%
Present	22	(48.9 %)
Lobar	14	(63.6%)
Segmental	3	(13.6%)
Lobar & segmental	5	(22.7%)
Not present	23	(51.1 %)
Total	45	(100%)

After conducting a differentiation test to compare the level of coagulation factors and thrombocyte level between those with and without lung embolism, there was no significant difference found between the two groups ($p > 0.05$) (Table 4).

Table 4. Correlation between coagulation factors and pulmonary embolism incidence in moderate-severe COVID-19 patients

	COVID-19 patients with pulmonary embolism		
	Mean ± SD	Median	Min - Max
WELL's score	0.23 ± 0.57	0.00	0.00-2.50

Coagulation Factors	Pulmonary Embolism (Mean ± SD)		p-value
	Present	Not Present	
PT	14.21 ± 0.39	14.01 ± 0.38	0.498
APTT	29.9 ± 1.37	31.3 ± 1.83	0.545
D-dimer	1366.17 ± 220.32	986.54 ± 116.94	0.637
Fibrinogen	408.18 ± 22.64	438.26 ± 14.11	0.089
Thrombocyte	202,909 ± 73,053	228,174 ± 75,714	0.241

*ETA Test

Table 4 shows WELL's score results of moderate-severe COVID-19 patients who experienced pulmonary embolism with mean ± SD 0.23 ± 0.57 and with the conclusion being PE low risk (<2 points) or PE unlikely (0-4 points).

Chest CT Scan Image of a COVID-19 Patient with Pulmonary Embolism

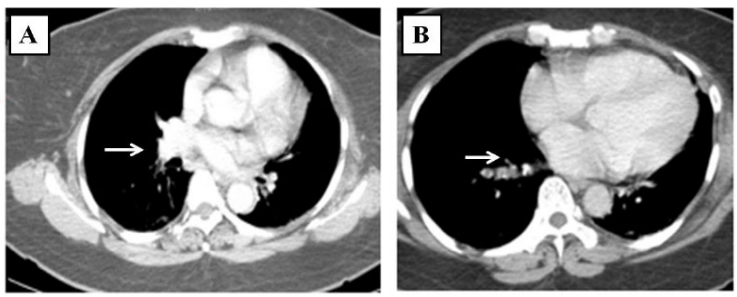

Figure 1. (A) Enhanced CT shows a filling defect in the right main pulmonary artery (white arrow) and (B) a small branch of the right pulmonary artery (white arrow) due to pulmonary embolism.

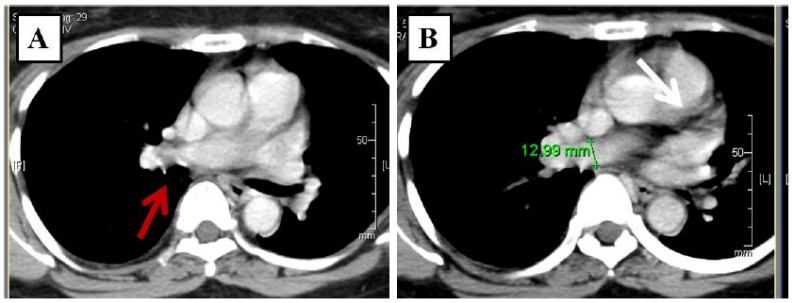

Figure 2. (A) Filling defect in the right pulmonary artery (red arrow), (B) normal-size main pulmonary artery and right pulmonary artery.

DISCUSSION

Coagulopathy in the forms of venous and arterial thromboembolism appears as one of the worst COVID-19 sequel and has the worst prognosis. Extremely high inflammatory response triggers thromboinflammation through cytokine storm, complement system activation, and endotheliitis. In addition, the virus may activate a coagulation cascade.[10]

This study reported average levels of PT and APTT. This may have been possible with COVID-19 due to the release of cytokines and tissue damage to the endothelium that releases tissue factor (TF). TF is a transmembrane protein and an FVIIa/FVII/cofactor that may activate the coagulation cascade. A slight increase in prothrombin time in CAC (especially severe/end-stage disease) may indicate TF pathway activation (extrinsic). The endogenous pathway, on the other hand, does not show activation, which means normal APTT levels.

The prolongation of APTT and PT can occur in patients who experienced severe COVID-19 levels, but the increase is not as severe as bacterial sepsis or disseminated intravascular coagulation (DIC). In addition, a study by Henry, *et al*. (2020) revealed that patients who experienced fatal and severe COVID-19 tend to have significantly higher coagulation parameters (especially prothrombin).[11] Bintoro, *et al*. (2021) reported in their study that there was an increase in APTT (albeit statistically insignificant) and a significant increase in prothrombin ($p < 0.05$) in a group of deceased patients.[12]

This study found elevated coagulation factors, D-dimer, and fibrinogen values in moderate-severe COVID-19 patients, with mean ± SD 1172.14 ± 838.95 and 423.56 ± 88.91, respectively. This is caused by a series of cleaving in which proteolysis coagulation changes circulation and inactive factor becomes activated. Two pathways reach the point of convergence where activated factor X cleaves prothrombin to form thrombin. Thrombin then cleaves fibrinogen resulting in fibrinogen monomers which quickly polymerize to stabilize aggregate thrombosis and form a thrombus.[13]

The fibrinolysis system will work to release tissue plasminogen activator (tPA) from endothelial, causing tPA-activated plasminogen to form plasmin. This plasmin degrades fibrin and produces D-dimer. The higher D-dimer elevates, the broader the thrombosis process will be. The resulting condition is called pulmonary intravascular coagulopathy (PIC) in the macrovascular and microvascular. This process aims to localize the virus and prevent it from spreading. If the process continues, IL-1, IL-6, and TNF-α cytokines will further increase. This cytokine inhibits anticoagulants such as ATIII, protein C, and protein S, leading to unstoppable thrombin formation and more fibrin cleaving from fibrinogen.[13]

Han, *et al*. (2020) reported that the increase in D-dimer and fibrinogen among COVID-19 survivors compared to healthy control was average D-dimer 10,400 vs. 260 ng/mL (unit DDU/FEU unreported), and average fibrinogen 500 vs. 290 mg/dL.[14] Fibrinogen degradation product (FDP) was also increased significantly, i.e., 34.8 compared to 1.6mg/L. D-dimer and FDP went up as the severity of COVID-19 progressed, but the fibrinogen level remained high. The significant increase in D-dimer might reflect lung artery thrombosis and fibrinolysis. D-dimer suggested the presence of cross-link clots by FXIIIa, fibrin clot formation, and fibrinolysis. A temporary increase in D-dimer indicated the progressive severity of the COVID-19 infection and could be used as a predictor that more aggressive critical care would be necessary.[15]

In this study, the mean ± SD of thrombocyte value in moderate-severe COVID-19 patients was 215,822 ± 74,676. Systematically, thrombocytopenia was detected in 41.7% of COVID-19 patients (incidence varied based on the disease severity), and it was generally mild (general total 100-150x10^9/L). Mild thrombocytopenia had been detected in 58-95% of severe COVID-19 patients. Patients with severe symptoms had a total thrombocyte count of 23x10^9/L to 31x10^9/L, lower than moderate/non-severe cases. Acute

thrombocytopenia was rarely reported in COVID-19 patients unless it is related to certain conditions, such as immune thrombocytopenic purpura.[15]

In this study, 22 (48.9%) moderate-severe COVID-19 patients were found with lung embolism who experienced hypercoagulation as evidenced by IV contrast thorax CT scan, while the remaining 23 patients (51.1%) were not. Based on the location of the embolism, 14 (63.6%) were found in the lobar, three (13.6%) in the segmental, and five (22.5%) in both lobar and segmental. This high incidence meant pulmonary embolism occurred in almost half of the subject's variables.

In two retrospective cohort studies, the incidence of PE in SARS-CoV-2 positive patients was 1.1% and 3.4%, respectively, regardless of hospitalization. The evidence of pulmonary embolism was found in 23-30% of patients undergoing CTA imaging.[16,17] In a prospective observational study of 150 patients treated in four intensive care rooms in two different hospitals in France, 16.7% of patients developed PE despite preventing thrombosis.[18] The study also reported that thromboembolism was found more frequently in patients with COVID-19 with acute respiratory distress syndrome (ARDS). A retrospective cohort of 184 COVID-19 patients treated in the intensive care unit (ICU) at three Dutch hospitals revealed that 13.6% of patients developed pulmonary embolisms even with anticoagulant therapy.[19] Interestingly, changing the follow-up period from one week to two weeks increased the incidence of PE to 33.3%. Poissy, *et al*. (2020) reported that 20.6% of patients treated in ICU in France showed that despite anticoagulant therapy, they developed pulmonary embolism within a median of six days after admission to ICU.[20]

Immune thrombosis is an innate immune system component caused by pathogens or cell damage, and coagulation activation is secondary to inflammation, resulting in the formation of microthrombi in small blood vessels. This interaction between coagulation activation, innate immune system, and endothelial dysfunction has been demonstrated in COVID-19. Moreover, as the understanding of SARS-CoV-2 deepens, it becomes clear that immunothrombosis plays an essential role in the severe cause of COVID-19.[21]

Firstly, after performing a differentiation test to compare the levels of coagulation factors and the level of thrombocyte between the presence and absence of PE, there was no significant difference between the two groups (p-value = 0.05). This might be because the sample group of moderate degree and severe degree in this study were not separated. Hence, the coagulation factors and the lung embolism occurrence of the two groups did not differ significantly. Secondly, despite the increase in coagulation disorders, especially D-dimer, no pulmonary embolism was found. This could be due to the inability of a thorax CT scan with IV contrast to detect any possible formation of microthrombi inside the microvascular. The notable finding in this study was that pulmonary embolism did occur in 48.9% of the moderate-severe COVID-19 patients despite no significant correlation between PE and coagulation factors. It shows that, although it did not require ICU treatment, the risk of pulmonary embolism was relatively high in this study.

Similar results were reported in the study conducted by Graziani, *et al*. (2021) where nine of 11 patients with elevated D-dimer but average/lower levels of other coagulation factors had distal thrombosis in their lower pulmonary arterial branch shown in their CTPA images.[22] None of the patients showed any signs of worsening respiratory problems, and some of them did not even receive oxygen therapy and breathed in regular room air. The parameters identified that stable COVID-19 patients increased the risk of concurrent pulmonary arterial thrombosis.[22] Elevated D-dimer was proven to correlate with the thrombosis level in COVID-19.[23–25] Patients with COVID-19 infection had a higher D-dimer value of >2660 with a 100% sensitivity (95%CI 88-100) and specificity of 67% (95%CI 52-79) to have lung embolism based on CTPA imaging.[5]

A state of hypercoagulability that plays a role in thrombosis, extensive capillary thromboembolism, and vascular and endothelial injury is directly responsible for microvascular thrombosis in situ.[26] Hemodynamic effect of lung thrombosis facilitated a reduction of the primary pulmonary vasodilation in some COVID-19 patients. Dual-energy CT shows pulmonary artery dilation in COVID-19 pneumonia. Ackerman, *et al*. (2020) also reported a high rate of pulmonary microthrombosis in COVID-19 patients.[27] Following a complete postmortem full-body examination, a large thrombus blocking the main pulmonary artery was found to be the cause of death. Histopathology analysis displayed heterogeneous patterns from pathological changes in pulmonary tissues with numerous vascular thrombi.[6]

Similar results were also reported in a previous study where thrombosis incidence increased from 9.2% to 15% in non-ICU patients.[29] However, the rate of pulmonary embolism caused by bacterial or viral pneumonia was just 1% to 2.6%. High pro-inflammatory and anti-fibrinolytic states observed in patients with a more severe infection triggered the forming of thrombosis in COVID-19 patients.[28]

This study showed that WELL's score of moderate-severe COVID-19 patients experiencing pulmonary embolism with mean ± SD 0.23 ± 0.57 with PE low risk (<2 points) or PE unlikely (0-4 points). The

risk score, such as the WELL's score, aims at predicting a patient's risk factor of developing VTE, PE likely if the score>4 and PE unlikely if the score <4.[29] One study that evaluated the WELLs score with a fixed D-Dimer limit of 500ng/mL to diagnose PE in patients (suspected) with COVID-19 suggested that 74% patients in their study had a WELL's score with low probability for PE.[30] However, this had limited use in ruling out PE; only 2% of patients had negative D-dimer. Another study stated that even if there were no risk for PE, i.e., WELL's score <4, it could not guarantee there would not be a possibility of PE development.[31] D-dimer test could further ensure the exclusion of pulmonary embolism diagnosis.

CONCLUSION

This study found pulmonary embolism in patients with a moderate-severe degree of COVID-19 who had hypercoagulation confirmed by a thorax CT scan with IV contrast. Although there was no significant correlation with coagulation factors, this incidence was considerably high. Half of the study variables developed pulmonary embolism. It showed that the risk of PE was relatively high in this study despite the patients not needing ICU treatment.

WELL's score did not completely rule out the possibility of pulmonary embolism in COVID-19 cases. However, elevated D-dimer and confirmed image from IV contrast thorax CT scan can help diagnose PE in COVID-19 patients. In situations of limited resources/facilities, a thorax CT scan with IV contrast can substitute/replace CTPA as the gold standard in pulmonary embolism detection/identification. A normal thorax CT scan with IV contrast is recommended for severe and moderate cases of COVID-19.

LIMITATIONS

It is a single-center study in Sumatera Utara, Indonesia. Further studies could be conducted in different settings.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conseptualizing and validating data: WBP. Checking grammar: NNS. Investigating data: SPT. Analyzing data: NNS and MA. Supervising and pulmonary consulting: RJS and AGI. Methodology writing: PCE. Preparing manuscript: WBP, NNS, SPT, MA, NDL, IS, and PCE. All authors contributed and approved the final version of the manuscript.

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