Journal of Health and Medical Sciences

Jeyabaladevan, Priyancaa, and Jeyabaladevan, Sharenja. (2021), Pulmonary Embolism Detection in COVID-19 Patients. In: *Journal of Health and Medical Sciences*, Vol.4, No.3, 50-57.

ISSN 2622-7258

DOI: 10.31014/aior.1994.04.03.178

The online version of this article can be found at:
https://www.asianinstituteofresearch.org/

Published by:
The Asian Institute of Research

The Asian Institute of Research *Journal of Health and Medical Sciences* is a peer-reviewed International Journal. The journal covers scholarly articles in the fields of Medicine and Public Health, including medicine, surgery, ophthalmology, gynecology and obstetrics, psychiatry, anesthesia, pediatrics, orthopedics, microbiology, pathology and laboratory medicine, medical education, research methodology, forensic medicine, medical ethics, community medicine, public health, community health, behavioral health, health policy, health service, health education, health economics, medical ethics, health protection, environmental health, and equity in health. As the journal is Open Access, it ensures high visibility and the increase of citations for all research articles published. The *Journal of Health and Medical Sciences* aims to facilitate scholarly work on recent theoretical and practical aspects of Health and Medical Sciences.

ASIAN INSTITUTE OF RESEARCH
Connecting Scholars Worldwide

ASIAN INSTITUTE OF RESEARCH
Connecting Scholars Worldwide

The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.4, No.3, 2021: 50-57
ISSN 2622-7258

DOI: 10.31014/aior.1994.04.03.178

Pulmonary Embolism Detection in COVID-19 Patients

Priyancaa Jeyabaladevan[1], Sharenja Jeyabaladevan[2]

[1] Barking, Havering and Redbridge University Trust
[2] Chelsea and Westminster Hospital NHS Foundation Trust

Correspondence: Priyancaa Jeyabaladevan. 27 Stradbroke Grove, Clayhall, Ilford, Essex. IG5 0DN.
Email: p.jeyabaladevan@nhs.net

Abstract
Background: A clinically important impact of Coronavirus Disease 2019 (COVID-19) is the increased likelihood of thromboembolism, mainly pulmonary embolism (PE). To screen for these complications a biochemical marker, D-dimer, is usually done. There is a plethora of research validating the use of D-dimer cutoff levels in non-COVID-19 patients, however less so in the COVID-19 population. Aim: To determine the number of suspected COVID patients with D-dimer ≥ 0.5 and PE reported on CTPA. Methods: Non-interventional single-centre retrospective clinical correlational study. Patient cohort was patients admitted with suspected COVID-19 over a 5-week period. N=690. Results: 76.5% of suspected COVID-19 patients were PCR positive. 40% of these patients had a CTPA completed with 19% reported to have a PE. 52% of patients had a D-dimer value ≥ 0.5 10.6% patients had a PE with a D-dimer ≥ 0.5. Conclusion: Nationally, hospitals are adopting existing D-dimer cut off levels to rule out PEs, however this leads to a large proportion of admitted COVID-19 patients having possibly unnecessary computed tomography pulmonary angiogram. This study highlights that majority of patients with D-dimers above the cut off level have negative PEs and contributes to the notion that standard D-dimer cutoffs are insufficiently accurate to be used as a standalone test in diagnosis in the context of an underlying SARS-CoV-2 infection.

Keywords: Coronavirus Disease 2019, COVID-19, Pulmonary Embolism, CTPA

1. Introduction

1.1 Background

The first case of severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) was described in December 2019 and by March 2020 it became the root of a global health emergency (Schulman, Hu and Konstantinides, 2020). Already, there is a vast amount of research investigating the mechanisms of the disease process, its effects on our bodies and the optimal treatments, but there remains much unknown. Infection with SARS–CoV–2 can be asymptomatic, but in some it leads to a deregulated immune response with multiorgan failure and critical illness (Al-Ani, Chehade and Lazo-Langner, 2020., Huang et al., 2020., Chen et al., 2020). Aside from the fundamental respiratory symptoms of the disease, there is evidence that patients are in a hypercoagulable state. This increases the risk of thromboembolism and overall has increased mortality risk (Al-Ani, Chehade and Lazo-Langner, 2020., Danzi et al., 2020). The rate of thromboembolism in patients with SARS-CoV-2 is varied in literature. Some

studies suggest 20-30% in confirmed cases while others can be as high as 40-70% (Minet et al., 2015., Malato et al., 2010). Studies suggest that the more severe the disease and involving needs for admission correlates with increased likelihood of hypercoagulation and thromboembolic complications. Some studies show a higher risk of mortality in Coronavirus Disease 2019 (COVID-19) patients with thromboembolism whereas other studies deny an association (Abou-Ismail et al., 2021., Qin et al., 2020). With such varied reporting, the rate of thromboembolism in COVID–19 remains unidentified. It was noted many patients were undergoing computed tomography pulmonary angiography (CTPA) for elevated D- Dimers, but majority reported as negative for PE. The objective of this study is to examine the prevalence of pulmonary embolism (PE) reported in patients with suspected COVID -19.

1.2 Pathogenesis of COVID-19

COVID-19 relies on the interaction between thrombosis and inflammation, causing a hypercoagulable state. SARS– CoV–2 enters the alveolar epithelium via angiotensin converting enzyme 2 (ACE2) receptors, causing excessive inflammatory cytokine and chemokine release. This further activates epithelial cells, monocytes, and neutrophils. Additionally, endothelial cells are directly infected through the ACE2 receptor, and the coagulation cascade is triggered, producing thrombin and fibrin clot. Platelets and the protease- activated receptor pathway is activated, which further stimulates inflammation. The interaction between thrombosis and inflammation puts the body in a high proinflammatory state, leading to local coagulation points (Malato et al., 2010). Research shows in COVID–19, inflammatory indicator IL-6 is elevated. There is correlation between raised IL-6 and raised fibrinogen levels, further supporting the theory of inflammatory thrombosis. They hypercoagulable state leads to further macrovascular and microvascular thrombosis (Abou-Ismail et al., 2021., Qin et al., 2020., Levi, van der Poll and Büller, 2004). Several studies found that most patients with COVID-19 infection suffered from lymphopenia, especially CD4+ cell reduction, and which is more obvious in severe patients. The weakening of the immune system will increase inflammatory response, promote cytokine storm production, worsen the damaged tissues, and increase risks of thromboembolism (Huang et al., 2020. Malato et al., 2010., Xu et al., 2020).

1.3 Risk Factors for Thrombosis in COVID-19

Increased age, obesity, immobilization, smoking and co-morbidities such as previous thromboembolism, chronic kidney disease, malignancy, heart/respiratory failure and being of an ethnic monitory background are risk factors for thromboembolism in COVID-19. This combined with hypoxia, sepsis, pre-eclampsia and post-partum infection can further increase the risk of thromboembolism (Xu et al., 2020). A recent study suggests that in obesity, adipose tissue acts as a potent inflammatory reservoir for the replication of SARS-CoV-2, where the inflammatory response is more prominent in obese compared with lean patients (Vaughan et al., 2020). For those critically unwell with COVID-19, a surge of inflammatory mediations in adjunct with steroid administration as part of treatment can lead to increased coagulation and increase thrombosis complications. Studies report that acute respiratory distress syndrome (ARDS) patients secondary to COVID-19 have more thrombosis complications, mainly pulmonary embolisms, compared those with ARDS secondary to non-COVID-19 pathology (Helms et al., 2020).

1.4 Biometrics associated with thromboembolism

Biochemical tests can be taken as a reference in the risk assessment for thromboembolism. Abnormal coagulation parameters in COVID–19 patients are usually associated with poor prognosis (Terpos et al., 2020). Furthermore, significantly elevated D-Dimer is correlated with increase death secondary to thromboembolism in COVID -19. A significant increase in D-dimer is a sign of activation of coagulation and fibrinolysis and is a good indicator for identifying high risk populations with possible thromboembolism (Tang et al., 2020). One study concluded that D-dimer levels >1.5μg/mL had a sensitivity of 85% and a specificity of 88.5% with a negative predictive value of 94.7% for thromboembolism (Cui et al., 2020). A meta-analysis of six Chinese studies showed that the mean D-dimer level was 0.44 μg/mL higher (95% CI: 0.23–0.66) in patients with severe versus non-severe disease, and 5.91 μg/mL higher in non-survivors than in survivors (Jin et al., 2020). However, it should be considered that D-

dimer can also be elevated in other conditions, such as pregnancy, postoperatively, malignancy, and sepsis, which needs to be measured with the clinical context (Middeldorp et al., 2021).

2. Aim

To determine the number of suspected COVID patients with D-dimer ≥ 0.5 with a CTPA reporting PE

3. Methods

This is a non-interventional single-centre retrospective clinical correlational study. The inclusion period for this study was patients admitted to a district general hospital with suspected COVID-19 between 6th December 2020 and 16th January 2021. The recorded data sets were sex, D-dimer, C-reactive protein (CRP), COVID PCR result, CTPA request, CTPA result, heart rate on admission and death. Sex, D-dimer, CRP and COVID PCR results were extracted from CyberLab. CTPA request and results from PACS system. Heart rate was extracted from vitalPACS and death was identified using EPRO. Statistical analysis was conducted using Microsoft Excel. N=690.

4. Results

Of 690 patients, the average age was 61.9 years, with the youngest being 20 years and the eldest being 101 years. 42.9% (296) were female and 57.1% (394) were male. The lowest admission CRP was <1 and the highest being 760. 76.6% (528) of patients were PCR COVID -19 positive and 23.5% (162) were PCR negative. 1.1% (8/690) died during admission with 88% (7/8) of them being PCR positive and 12.5% (1/8) of them having a PE.

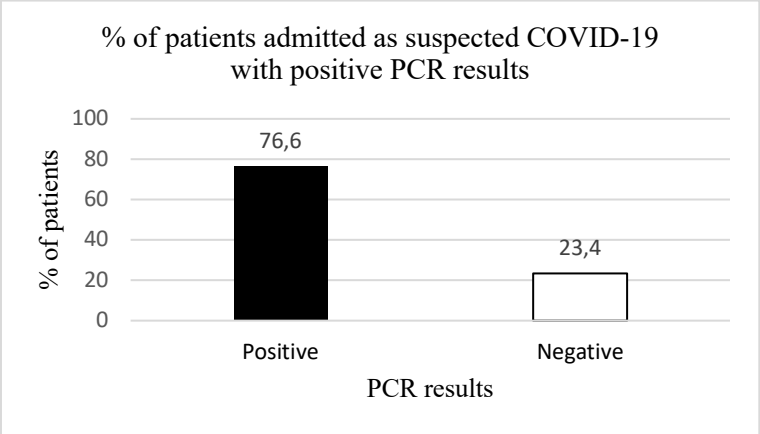

Figure 1. Percentage of patients admitted as suspected COVID-19 with positive PCR results.
76.6% (528/690) of suspected COVID -19 patients were PCR positive. 23.4% (162/690) were PCR negative.

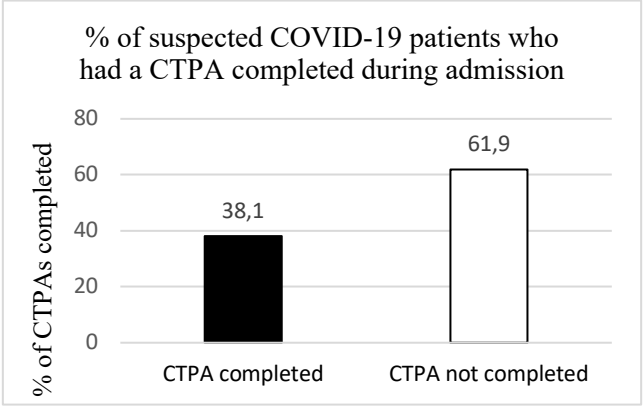

Figure 2: Percentage of suspected COVID-19 patients who had a CTPA completed during admission
38.1% (263/690) of patients admitted with suspected COVID – 19 had a CTPA completed. 61.9% (427/690) did not have a CTPA completed.

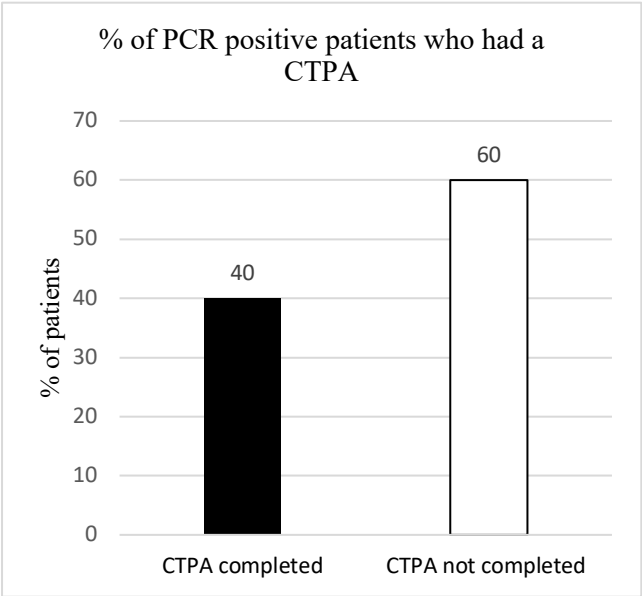

Figure 3: Percentage of PCR positive patients who had a CTPA

40% of PCR positive patients (211/258) had a CTPA completed and 60% (317/528) did not have a CTPA completed.

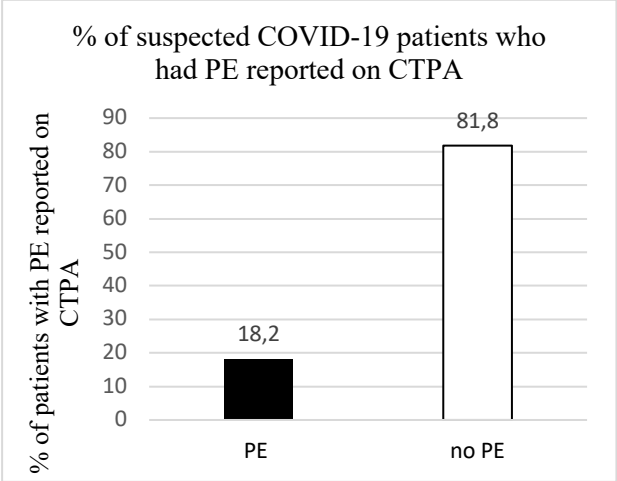

Figure 4: Percentage of suspected COVID-19 patients who had PE reported on CTPA

18.2% (48/263) of those who had CTPA had a PE reported. 81.8% (215/263) had no PE reported.

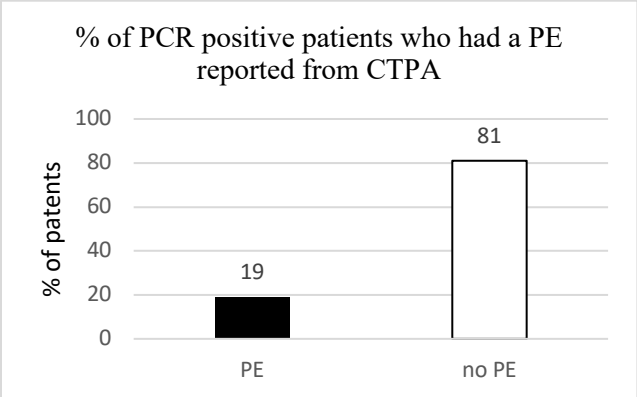

Figure 5: Percentage of PCR positive patients who had a PE reported from CTPA

19% (40/211) had a PE reported on CTPA. 81% (171/211) had no PE reported.

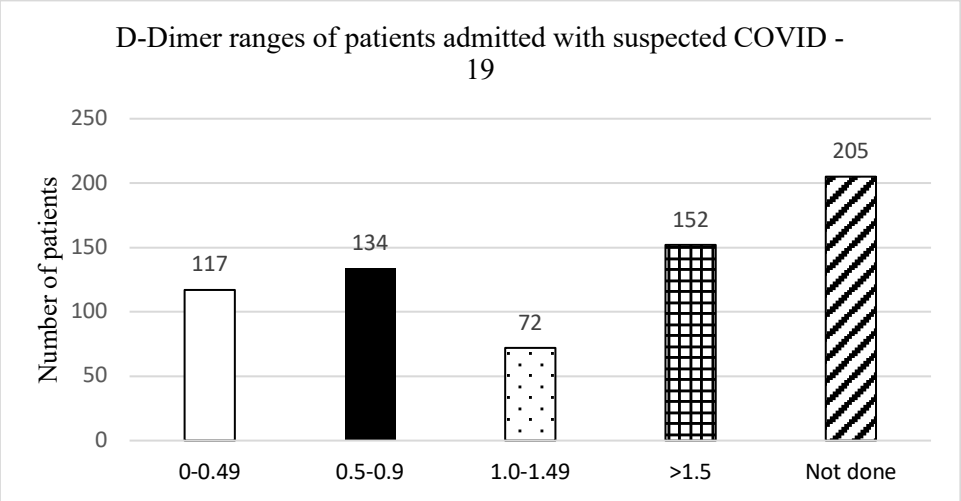

Figure 6: D-Dimer ranges of patients admitted with suspected COVID -19

117 patients had a D-dimer value between 0 – 0.49. 134 patients had a D-dimer value between 0.5-0.9. 72 patients had a D-dimer value between 1.0-1.49. 152 patients had a D-dimer value >1.5. 205 patients did not have a D-dimer requested throughout the admission.

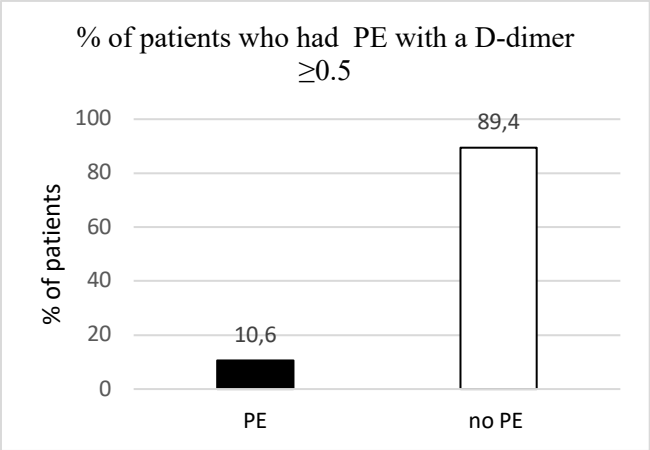

Figure 7. Percentage of patients who had PE with a D-dimer ≥0.5

10.6% (36/358)of patients with a D-dimer ≥0.5 had a PE reported on CTPA. 89.4% (320/358) did not have PE reported with a D-dimer <0.5.

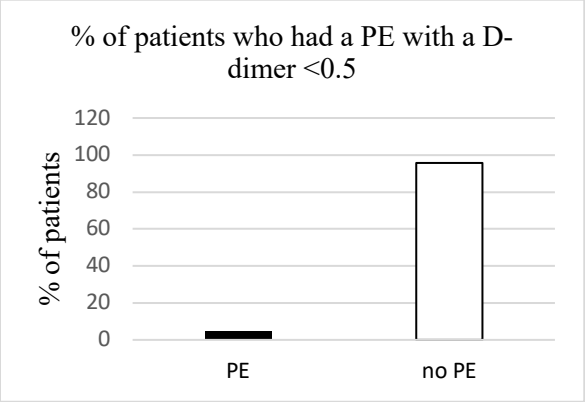

Figure 8. Percentage of patients who had PE with a D-dimer <0.5

4.3% (5/117) of patients with a D-dimer <0.5 had a PE and 95.7% (112/117) patients with a D-dimer <0.5% did not have a PE.

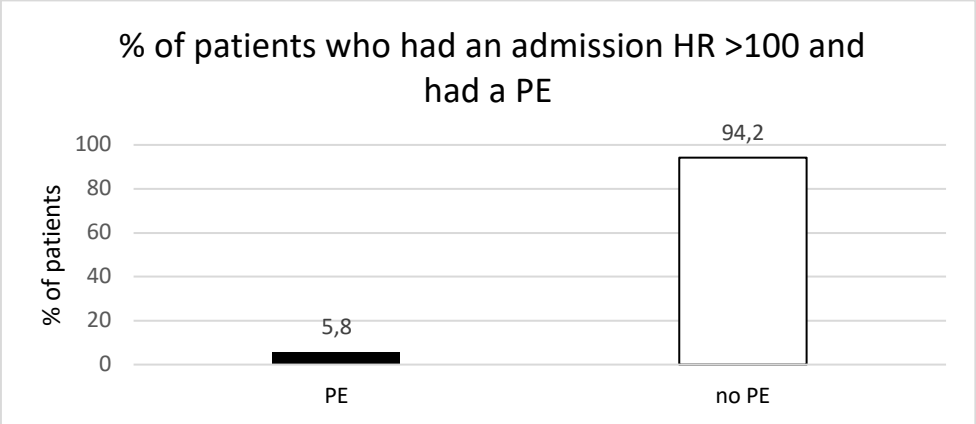

Figure 9. Percentage of patients who had an admission HR >100 and had a PE
5.8% (4/70) of patients with an admission HR >100 had a PE and 94.2% (66/70) did not have a PE.

5. Discussion

This hospital's local trust guidelines suggest that if the D-Dimer value is ≥0.5, a hypercoagulable state should be suspected, however only 10.6% of patients with a D-dimer ≥0.5 had a PE reported on CTPA. Considering the radiation dose of a CTPA is close to that of an invasive pulmonary angiography and there are risks associated with contrast administration, there is a need for a wider screening strategy for PE. An example of an existing strategy is the YEARS criteria (van der Hulle et al., 2017). It requires information such as clinical signs of DVT, evidence of hemoptysis and whether PE is the most likely diagnosis. Alongside this, one must consider the clinical symptoms and signs of PEs, such as tachycardia, pleuritic chest pain, shortness of breath and desaturations (Rosovsky et al., 2020, MDCalc, n.d.). In the context of COVID -19 many of these symptoms overlap. In a non – infective state, those that are symptomatic +/- have an elevated D-dimer should have a subsequent CTPA. However, it is unknown whether similar D-dimer thresholds can be applied in COVID-19 patients, because of the hyperinflammatory state with endothelial activation and as a result,
High D-dimer level.

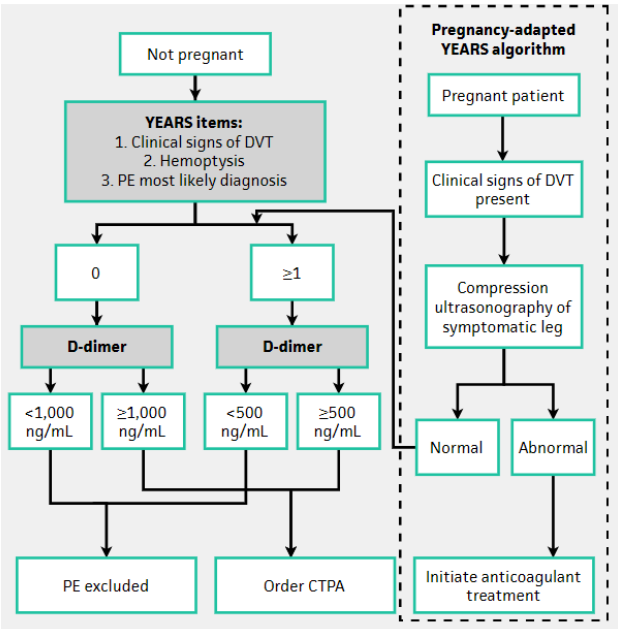

Figure 10: YEARS Criteria
Flow diagram depicting how to use the YEARS algorithm if suspecting pulmonary embolism (19).

5. Conclusion

The SARS-CoV-2 pandemic raises new challenges in the diagnosis of a PE. The pro-inflammatory state puts patients in a hypercoagulable state but also will increase their D-dimer. In non-COVID patients, simple and minimally invasive diagnostic algorithms can safely rule out PE, however similar algorithms are urgently needed for COVID-19 patients. Currently, clinicians err on the side of caution and will likely go for CT based imaging if D-dimer levels are above 0.5 µg/mL and the patient is symptomatic, however the radiation dose and effects of contrast must be considered. Mouhat et al. conclude a D-dimer cut-off of 2.59µg/mL in COVID-19 patients should be used to consider patients for a CTPA (Mouhat et al., 2020). However, further validation is required and currently it is not clinically relevant and cannot be safely applied. A strategy of overcoming this would be to use an age-adjusted D-dimer. Age adjusted D-dimers were initially used as in elderly patients a cutoff of 0.5µg/mL is rarely truly negative. Retrospective validation suggests that 'and age per 10' cutoff in patients above 50 years is safe, i.e. a patients aged 60 years would have an age adjusted D-dimer of 0.6µg/mL. Ultimately, whether similar D-dimer thresholds can be applied to COVID-19 patients is largely unknown, but this study contributes to the notion that standard D-dimer cutoffs are insufficiently accurate to be used as a standalone test in diagnosis of PE in the context of an underlying SARS-CoV-2 infection

Funding: None
Ethical Committee approval: Not required
Conflicts of Interest: None

References

Schulman, Sam et al. "Venous Thromboembolism in COVID-19." Thrombosis and haemostasis vol. 120,12 (2020): 1642-1653. doi:10.1055/s-0040-1718532

Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res.* 2020;192:152–160.

Huang C, Wang Y, Li X.Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China *Lancet* 2020395(10223):497–506

Chen N, Zhou M, Dong X.Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study *Lancet* 2020395(10223):507–513.

Danzi G B, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J.* 2020;41(19):1858

Minet C, Potton L, Bonadona A. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care.* 2015;19:287.

Malato A, Dentali F, Siragusa S. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. *Blood Transfus.* 2015;13(04):559–568.

Abou-Ismail M Y, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res.* 2020;194:101–115.

Qin C, Zhou L, Hu Z. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis.* 2020;71(15):762–768.

Levi M, van der Poll T, Büller H R. Bidirectional relation between inflammation and coagulation. *Circulation.* 2004;109(22):2698–2704.

Xu X W, Wu X X, Jiang X G. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ.* 2020;368:m606.

Vaughan C J, Cronin H, Ryan P M, Caplice N M. Obesity and COVID-19: a Virchow's triad for the 21st century. *Thromb Haemost.* 2020 doi: 10.1055/s-0040-1714216.

CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis) . Helms J, Tacquard C, Severac F. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46(06):1089–1098.

Terpos E, Ntanasis-Stathopoulos I, Elalamy I. Hematological findings and complications of COVID-19. *Am J Hematol.* 2020;95(07):834–847.

Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(04):844–847.

Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(06):1421–1424.

Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and impact of coagulation dysfunction in COVID-19 in China: a meta-analysis. *Thromb Haemost.* 2020 doi: 10.1055/s-0040-1714369.

Middeldorp S, Coppens M, van Haaps T F. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020;18(08):1995–2002.

van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289-297.

Rosovsky RP, Grodzin C, Channick R, et al.Diagnosis and Treatment of Pulmonary Embolism During the Coronavirus Disease 2019 Pandemic: A Position Paper From the National PERT Consortium. Chest 2020; 158:

2021. [online] Available at: <https://www.mdcalc.com/years-algorithm-pulmonary-embolism-pe#next-steps> [Accessed 8 August 2021].

Mouhat B, Besutti M, Bouiller K, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. Eur Respir J 2020; 56: 2001811. doi:10.1183/13993003.01811-2020