Brief Report

An optimized D-dimer cut-off value to predict pulmonary thromboembolism in COVID-19 patients

Sophie Y. H. Engels[1]^, Ilonka H. P. A. A. van Veen[1]^, Matthijs Oudkerk[2,3]^, Job van der Palen[4,5]^, Marjolein A. Heuvelmans[1,3,6]^

[1]Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, The Netherlands; [2]Faculty of Medical Sciences, University of Groningen, Groningen, The Netherlands; [3]Institute for Diagnostic Accuracy, Groningen, The Netherlands; [4]Department of Epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands; [5]Section Cognition, Data and Education, Faculty of Behavioural, Management and Social Sciences, University of Twente, Enschede, The Netherlands; [6]University of Groningen, University Medical Centre Groningen, Department of Epidemiology, Groningen, The Netherlands

Correspondence to: Sophie Y. H. Engels, MD. Department of Pulmonary Medicine, Medisch Spectrum Twente, Koningsstraat 1, Enschede, 7512 KZ, The Netherlands. Email: syhengels@gmail.com.

Abstract: Pulmonary thromboembolism (PTE) is a common complication in coronavirus disease 2019 (COVID-19) patients. Elevated D-dimer levels are observed even in the absence of PTE, reducing its discriminative ability as a screening test. It is unknown whether conventional D-dimer cut-off values, as used in the YEARS algorithm, apply to COVID-19 patients. This study aimed to determine the optimal D-dimer cut-off value to predict PTE in COVID-19 patients. All confirmed COVID-19 patients with a computed tomography pulmonary angiography (CTPA) performed ≤5 days after admission due to suspicion of PTE between March 2020 and February 2021, at Medisch Spectrum Twente, The Netherlands, were retrospectively analyzed. The association between PTE and D-dimer levels prior to CTPA, and other potential predictors, was analyzed using logistic regression analyses. The optimal cut-off value was identified using receiver operating characteristic (ROC) curve analyses. In 142 patients, PTE prevalence was 20.4%. The optimal cut-off value was 750 ng/mL (sensitivity 100%; specificity 19.5%; negative predictive value 100%; positive predictive value 24.2%). In total, 15 of 113 (13%) patients without PTE had a D-dimer level ≥500 and <750 ng/mL. In our population of patients hospitalized with COVID-19, a D-dimer level <750 ng/mL safely excluded PTE. Compared to the YEARS 500 ng/mL cut-off value, 13% fewer patients are in need of a CTPA, with similar sensitivity. Future research is required for external validation.

Keywords: Pulmonary thromboembolism (PTE); thrombosis; coronavirus disease 2019 (COVID-19); computed tomography pulmonary angiography (CTPA); fibrin fibrinogen degradation products

Submitted Jun 04, 2023. Accepted for publication Sep 14, 2023. Published online Nov 27, 2023.
doi: 10.21037/jtd-23-870
View this article at: https://dx.doi.org/10.21037/jtd-23-870

Introduction

Pulmonary thromboembolism (PTE) is a common complication in coronavirus disease 2019 (COVID-19) patients, including pulmonary embolism and *in situ* pulmonary thrombosis (1,2). Elevated D-dimer levels are observed even in the absence of PTE, reducing its discriminative ability as a screening test (3). In these cases, elevated D-dimer levels can be explained by systemic microvascular thrombosis (4). However, microvascular thrombosis may also occur without D-dimer elevation (4).

^ ORCID: Sophie Y. H. Engels, 0000-0002-1367-7526; Ilonka H. P. A. A. van Veen, 0000-0003-4876-0482; Matthijs Oudkerk, 0000-0003-2800-4110; Job van der Palen, 0000-0003-1071-6769; Marjolein A. Heuvelmans, 0000-0002-5712-4085.

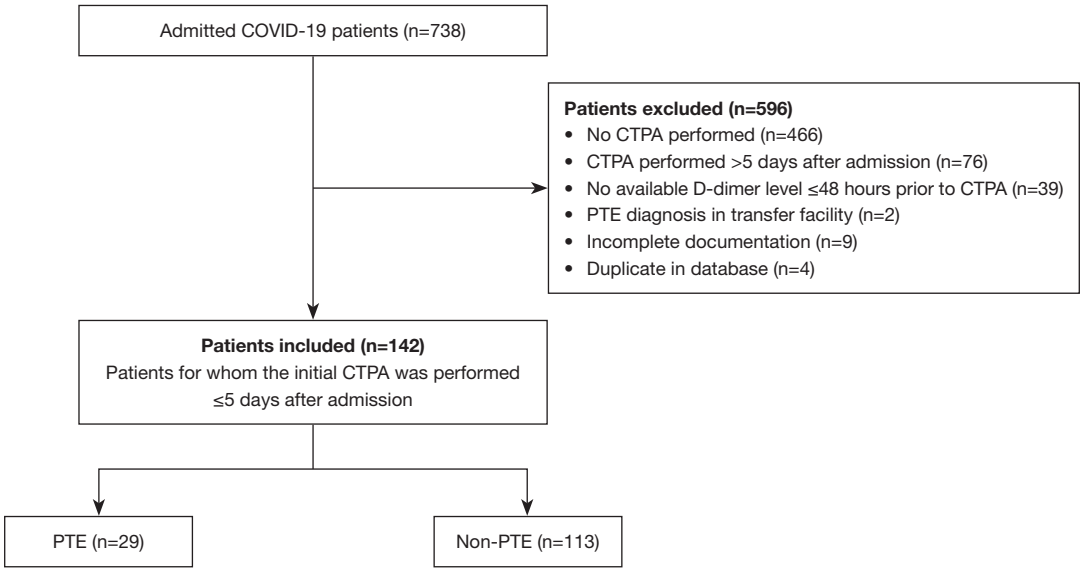

Figure 1 Flowchart of the study. COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiography; PTE, pulmonary thromboembolism.

The National Institute for Public Health of the Netherlands advised applying D-dimer cut-off values of locally used algorithms, e.g., the YEARS algorithm, for COVID-19 patients (5). The YEARS algorithm is a widely used clinical decision rule which uses three of the Wells criteria, i.e., YEARS items, and variable D-dimer thresholds (6). Nevertheless, whether conventional cut-off values do apply to COVID-19 patients is unknown (7). This study aimed to determine the optimal D-dimer cut-off value to predict PTE in COVID-19 patients. We present this article in accordance with the STROBE and TRIPOD reporting checklists (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-870/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The local Ethics Committee of Medisch Spectrum Twente approved this retrospective analysis of prospectively collected data and waived the need for informed consent (No. K21-33). All collected laboratory results were part of routine care. Patient inclusion was based on the COREON Statement, a statement of sharing patient data in observational scientific research in emergency situations. This states that data from patients who have objected will not be used. All confirmed COVID-19 patients with a computed tomography pulmonary angiography (CTPA) performed ≤5 days after admission due to suspicion of PTE between March 2020 and February 2021 at Medisch Spectrum Twente, Enschede, The Netherlands, were retrospectively analyzed. To finalize the discussion on the utility of D-dimer levels in COVID-19 patients, we routinely performed D-dimer measurements on admission and follow-up, as previously brought up by Oudkerk *et al.* (8). Given that the majority of COVID-19 patients had elevated D-dimer levels, even in the absence of PTE, and since PTE was not the most likely diagnosis as hypoxemia could be explained by COVID-19 itself, a D-dimer cut-off value of ≥1,000 ng/mL was primarily used in the Medisch Spectrum Twente. This value is derived from the YEARS algorithm (6). In case of doubtful clinical situations, it was possible to deviate from this cut-off value, namely in case of clinical deterioration, a sudden increase in D-dimer levels, and in case of discrepancy between severe hypoxemia and clinical presentation. Therefore, all patients with D-dimer levels ≥1,000 ng/mL or patients with D-dimer levels <1,000 ng/mL and doubtful clinical situations underwent CTPA.

Exclusion criteria were age <18 years, no available D-dimer level ≤48 hours prior to CTPA, and incomplete documentation (*Figure 1*). For all included patients, additional data at time of the CTPA was retrieved from the medical records, including hospitalization status, D-dimer level prior to CTPA, other laboratory results at the same date as the selected D-dimer level, and whether a patient

had symptoms of COVID-19 for more than ten days at time of the CTPA. The last variable was chosen since the third COVID-19 phase, i.e., hyperinflammatory phase, frequently emerges around disease day ten (9). This phase is characterized by a hypercoagulable state associated with thrombotic events (10). Regarding the D-dimer level selection, the D-dimer level at admission was chosen if a CTPA was performed ≤24 hours after admission; in all other cases the most recent D-dimer ≤48 hours prior to CTPA was chosen.

Statistical analysis

Continuous variables were described as mean with standard deviation or median with interquartile range (IQR) and compared using an unpaired *t*-test or Mann-Whitney *U* test. Categorical variables were described with numbers (n) and percentages (%). These variables were compared using Pearson's χ^2 tests or Fisher's exact tests, as appropriate. The association between PTE and D-dimer levels prior to CTPA, and other potential predictors, was analyzed using logistic regression analyses, with adjustment for potential confounders (probability for variable entry P≤0.10). Based on the final logistic regression model, diagnostic test parameters were calculated for different coordinates of the receiver operating characteristic (ROC) curve and the optimal cut-off value was chosen based on clinical meaningfulness. Statistical analyses were performed using IBM SPSS Statistics 27, 2020. P<0.05 was indicative of a significant difference.

Results

In total 142 COVID-19 patients [mean age 70±13 years, 88 (62%) men] were included (*Table 1*). Based on the CTPA, 29 of 142 (20.4%) patients were diagnosed with PTE. Forty-one patients underwent CTPA despite a D-dimer level <1,000 ng/mL. In this group of patients, 2 of 41 patients were diagnosed with PTE (D-dimer levels 760 and 816 ng/mL). Median D-dimer levels prior to CTPA were higher in patients with PTE than those without PTE, 7,279 ng/mL (IQR, 3,737–8,299 ng/mL) *vs.* 1,451 ng/mL (IQR, 816–2,695 ng/mL) (P=0.001). Additionally, a higher mean platelet count (274±115 *vs.* 232±91×10^9/L; P=0.042), mean white blood cell (WBC) count [(10.9±4.6)×10^9 *vs.* (8.4±4.0)×10^9/L; P=0.005] and median lymphocyte count [1.0×10^9/L (IQR, 0.7×10^9–1.3×10^9/L) *vs.* 0.7×10^9/L (IQR, 0.5×10^9–1.1×10^9/L); P=0.021] were observed in the PTE group. The variables '≥10 days symptoms of COVID-19 at time of CTPA', 'platelet count', and 'WBC count' had a relation of P≤0.10 with the occurrence of PTE and the D-dimer level prior to CTPA. Therefore, these variables were considered to be possible confounders. Binary logistic regression analysis was conducted using PTE grouping (PTE *vs.* non-PTE) as the dependent variable with 'D-dimer level prior to CTPA', '≥10 days symptoms of COVID-19 at time of CTPA', 'platelet count', and 'WBC count' as covariables. Logistic regression analyses indicated solely D-dimer level prior to CTPA to be a predictor for PTE [odds ratio: 1.05, 95% confidence interval (CI): 1.03–1.07, P<0.001] for every 100 ng/mL increase. The optimal D-dimer cut-off value was 750 ng/mL [sensitivity 29 of 29 (100%); specificity 22 of 113 (19.5%); negative predictive value 22 of 22 (100%); positive predictive value 29 of 120 (24.2%)]. The area under the curve (AUC) was 0.83 (95% CI: 0.74–0.92). The ROC curve is shown in *Figure 2*. In total, 15 of 113 (13%) patients without PTE had a D-dimer level ≥500 and <750 ng/mL.

Discussion

This study aimed to determine the optimal D-dimer cut-off value to predict PTE in COVID-19 patients. Based on our population of patients hospitalized with COVID-19, the optimal D-dimer cut-off level was 750 ng/mL. This cut-off value is higher than the widely used YEARS 500 ng/mL cut-off value, resulting in 13% fewer patients in need of a CTPA, with similar sensitivity. Previously reported cut-off values were commonly higher than 750 ng/mL (e.g., 2,590 and 1,700 ng/mL), however with lower sensitivity ranging between 83% and 89% (11,12). Solely Léonard-Lorant *et al.* (13) reported a higher cut-off value (2,660 ng/mL) with equal sensitivity. Compared to our study, they reported a higher percentage of intensive care unit patients and higher median D-dimer levels, however, diagnostic performance could not be evaluated due to an undescribed AUC. A more recent study by Revel *et al.* indicated that cut-off values ≥1,000 ng/mL had sensitivities below 90% (14).

It is questionable whether CTPA is the right imaging modality in COVID-19 patients because it mainly detects late-stage macrovascular thrombosis while microvascular thrombosis cannot be detected (4). Microvascular thrombosis can be detected with computed tomography perfusion, which is not routinely available (4). Therefore, therapeutic anticoagulation is indicated immediately in case of elevated or increasing D-dimer levels (4,5), we advise

Table 1 Demographic and clinical characteristics

Characteristics	All (n=142)	PTE (n=29)	Non-PTE (n=113)	P value
Age (years)	70±13	69±14	70±12	0.86
Male gender	88 [62]	19 [66]	69 [61]	0.66
BMI (kg/m^2)†	28±5	29±4	28±5	0.89
Comorbidities				
Obesity (>30 kg/m^2)†	48 [34]	10 [34]	38 [34]	0.88
Dyslipidaemia	13 [9]	3 [10]	10 [9]	0.73
Hypertension	65 [46]	16 [55]	49 [43]	0.26
Diabetes mellitus	38 [27]	7 [24]	31 [27]	0.72
Cardiac disease	42 [30]	7 [24]	35 [31]	0.47
Chronic pulmonary disease	32 [23]	4 [14]	28 [25]	0.21
Chronic liver disease	5 [3.5]	1 [3.4]	4 [3.5]	>0.99
Chronic kidney disease	7 [4.9]	1 [3.4]	6 [5.3]	>0.99
Dementia	3 [2.1]	1 [3.4]	2 [1.8]	0.50
Risk factors for PTE				
Prior VTE	7 [4.9]	1 [3.4]	6 [5.3]	>0.99
Pregnancy†	1 [0.7]	0 [0]	1 [0.9]	>0.99
Active cancer	14 [9.9]	2 [6.9]	12 [11]	0.74
Current smoking†	6 [4.2]	1 [3.4]	5 [4.4]	>0.99
Pre-hospital anticoagulant use‡				0.59
No use	97 [68]	22 [76]	75 [66]	
Therapeutic use	4 [2.8]	0 [0]	4 [3.5]	
Non-therapeutic use	41 [29]	7 [24]	34 [30]	
≥10 days symptoms of COVID-19 at time of CTPA†	65 [46]	18 [62]	47 [42]	0.055
CTPA during ICU admission	25 [18]	7 [24]	18 [16]	0.30
DVT during admission	5 [3.5]	1 [3.4]	4 [3.5]	>0.99
Laboratory parameters				
D-dimer level prior to CTPA (ng/mL)	1,658 (911–4,195)	7,279 (3,737–8,299)	1,451 (816–2,695)	0.001
Serum ferritin (μg/L)†	1,060 (598–1,975)	960 (369–1,640)	1,105 (647–2,060)	0.31
Haemoglobin (mmol/L)†	8.4±1.0	8.1±1.0	8.5±0.9	0.13
Platelet count (×10^9/L)†	241±98	274±115	232±91	0.042
White blood cell count (×10^9/L)†	8.9±4.2	10.9±4.6	8.4±4.0	0.005
Lymphocyte count (×10^9/L)†	0.8 (0.5–1.1)	1.0 (0.7–1.3)	0.7 (0.5–1.1)	0.021
Fibrinogen (g/L)†	5.9±1.8	5.6±2.2	6.0±1.6	0.62
Prothrombin time (s)†	11±1.0	12±1.3	11±0.9	0.12
C-reactive protein (mg/L)†	86 (44–177)	99 (69–199)	84 (42–159)	0.26
All-cause mortality	31 [22]	6 [21]	25 [22]	0.87

Data are presented as mean ± standard deviation, n [%], or median (interquartile range). †, missing data: body mass index n=32 (23%); obesity n=23 (16%); pregnancy n=88 (62%) because pregnancy does not apply to men; current smoking n=24 (17%); ≥10 days symptoms of COVID-19 at time of CTPA n=7 (5%); serum ferritin n=25 (18%); haemoglobin n=7 (5%); platelet count n=11 (8%); white blood cell count n=7 (5%); lymphocyte count n=15 (11%); fibrinogen n=117 (82%); prothrombin time 108 (76%); C-reactive protein n=4 (3%). ‡, low-molecular-weight heparin, vitamin K antagonists, and direct oral anticoagulants are categorized as therapeutic use; other forms of oral anticoagulation were categorized as nontherapeutic use. PTE, pulmonary thromboembolism; BMI, body mass index; VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiography; ICU, intensive care unit; DVT, deep venous thrombosis.

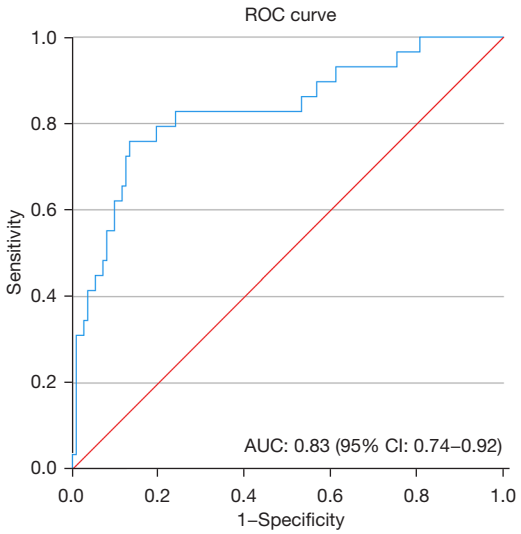

Figure 2 ROC curve of D-dimer level diagnostic performance. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

using a lower cut-off value than the previously mentioned published cut-off values (11-13). Limitations of our study are the single-center design, a relatively small sample size, and that results may not apply to all COVID-19 patients, e.g., non-hospitalized patients or patients with mild COVID-19 disease. Besides, results from this early pandemic study may not apply to patients nowadays as COVID-19 itself has evolved as a disease, partly due to a certain degree of population immunity. Future research is required for external validation. Clinical parameters, such as tachycardia and hypoxia, were not analyzed in this study. In future research, it may be relevant to investigate the influence and diagnostic value of these parameters as these are common clinical findings in patients with acute PTE. An odds ratio of 1.05 for every increase of 100 ng/mL in D-dimer level might not seem much, but given the huge range of possible D-dimer levels, it can be considered highly relevant. The D-dimer level is the best predictor for PTE in our study and it is statistically significant.

Conclusions

In our population of patients hospitalized with COVID-19, a D-dimer level <750 ng/mL safely excluded PTE. Compared to the YEARS 500 ng/mL cut-off value, 13% fewer patients are in need of a CTPA, with similar sensitivity.

Acknowledgments

An adapted version of the current abstract was presented at the ERS International Congress in September 2022.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE and TRIPOD reporting checklists. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-870/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-870/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-870/coif). I.H.P.A.A.v.V. has given presentations in collaboration with Sanofi Genzyme and Astra Zeneca, and participated in the advisory board of GSK, Astra Zeneca and Sanofi Genzyme. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The local Ethics Committee of Medisch Spectrum Twente approved this retrospective analysis of prospectively collected data and waived the need for informed consent (No. K21-33). All collected laboratory results were part of routine care. Patient inclusion was based on the COREON Statement, a statement of sharing patient data in observational scientific research in emergency situations. This states that data from patients who have objected will not be used.

References

1. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology 2021;298:E70-80.
2. Price LC, McCabe C, Garfield B, et al. Thrombosis and COVID-19 pneumonia: the clot thickens! Eur Respir J 2020;56:2001608.
3. Ventura-Díaz S, Quintana-Pérez JV, Gil-Boronat A, et al. A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study. Emerg Radiol 2020;27:679-89.
4. Oudkerk M, Kuijpers D, Oudkerk SF, et al. The vascular nature of COVID-19. Br J Radiol 2020;93:20200718.
5. Oudkerk M, Büller HR, Kuijpers D, et al. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. Radiology 2020;297:E216-22.
6. 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;390:289-97.
7. Conte G, Cei M, Evangelista I, et al. The Meaning of D-Dimer value in Covid-19. Clin Appl Thromb Hemost 2021;27:10760296211017668.
8. Oudkerk M, Büller HR, Kuijpers D, et al. d-Dimer and COVID-19. Radiology 2020;297:E343-4.
9. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405-7.
10. Ciaccio M, Agnello L. Biochemical biomarkers alterations in Coronavirus Disease 2019 (COVID-19). Diagnosis (Berl) 2020;7:365-72.
11. 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.
12. Thoreau B, Galland J, Delrue M, et al. D-Dimer Level and Neutrophils Count as Predictive and Prognostic Factors of Pulmonary Embolism in Severe Non-ICU COVID-19 Patients. Viruses 2021;13:758.
13. Léonard-Lorant I, Delabranche X, Séverac F, et al. Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. Radiology 2020;296:E189-91.
14. Revel MP, Beeker N, Porcher R, et al. What level of D-dimers can safely exclude pulmonary embolism in COVID-19 patients presenting to the emergency department? Eur Radiol 2022;32:2704-12.

Cite this article as: Engels SYH, van Veen IHPAA, Oudkerk M, van der Palen J, Heuvelmans MA. An optimized D-dimer cut-off value to predict pulmonary thromboembolism in COVID-19 patients. J Thorac Dis 2023;15(11):6317-6322. doi: 10.21037/jtd-23-870