National Institute for Health and Care Excellence

NICE guideline Venous thromboembolic diseases: diagnosis, management, and thrombophilia testing

[I] Evidence reviews for diagnosing VTE in people with COVID-19

NICE guideline NG158
Evidence reviews underpinning recommendations 1.1.6, 1.1.7, 1.1.11, 1.1.20 and 1.1.21 in the NICE guideline.

June 2023

Guideline version (Draft)

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ISBN: xxx

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1.1 Review question

In people with COVID-19 and suspected PE, can we safely rule out the need for further imaging based on a combination of clinical probability score and D-dimer assay?

1.1.1 Introduction

This is an update of NG158: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing focusing on diagnosing VTE in people with COVID-19. NG158 currently recommends that D-dimer testing should be used to rule out the need for imaging in someone with suspected PE with a Wells score that suggests PE is unlikely. D-dimer testing thresholds for ruling out imaging are specific to the type of D-dimer test used and can be fixed or age adjusted. This adjustment accounts for D-dimer levels increasing with age. The surveillance review conducted in 2022 highlighted that those with COVID-19 may present with symptoms that are similar to pulmonary embolism making the diagnoses difficult to distinguish. The review highlighted that D-dimer levels can be elevated in people with COVID-19 in the blood due to inflammation. There may also be a higher risk of blood clots associated with COVID-19. Therefore, guidance is needed on whether any modifications are required for the use of the Wells score for pre-test probability and D-dimers in the diagnosis of pulmonary embolism in people with COVID-19 and recent history of COVID-19. These modifications may include adjusting D-dimer threshold levels for people with COVID-19 whilst minimising the risk of missed PE diagnoses.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Adults with clinically suspected or confirmed COVID-19, or recent history of COVID-19 (within the past 6 months), and suspected PE
Index test	D-dimer test (age-adjusted or fixed test threshold) alone or in combination with a PE Wells score
Reference standard	MRI pulmonary angiography, ventilation-perfusion scan, CT pulmonary angiography, VTE event during 3 months of follow-up (for

	people discharged without imaging because they are considered low risk)
Outcomes	Diagnostic accuracy metrics: sensitivity/specificity, positive and negative likelihood ratios, area under the curve
Study type	Diagnostic accuracy cross-sectional studies and cohort studies.

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Methods specific to this review:

Use of pre-print (non-peer reviewed) publications

The search was expanded to include pre-print publication servers. This is because many authors chose to release manuscripts on pre-print servers to enable rapid dissemination of information during the COVID-19 pandemic.

Diagnostic accuracy measures

The committee chose likelihood ratios as the diagnostic accuracy measures to inform decision-making so GRADE was applied to these measures. The GRADE tables include measures of sensitivity and specificity which were presented to the committee to help with understanding the impact on false negative and false positive rates.

Where meta-analysis was not conducted, the following data was extracted where possible:

Likelihood ratios

- likelihood ratios and their corresponding 95% CI intervals were extracted from the individual studies where reported.

- likelihood ratios and their corresponding 95% CI intervals were calculated by the reviewer from 2x2 data where not reported in the study.

Sensitivity and specificity

- sensitivity and specificity and their corresponding 95% CI intervals were extracted from the individual studies where reported.
- sensitivity and specificity and their corresponding 95% CI intervals were calculated by the reviewer from 2x2 data where not reported in the study.

D-dimer measures

- Values of D-dimer were converted to units of ng/mL as this was the most reported unit.
- Where studies report D-dimer values as D-dimer units (DDU), these were converted to fibrinogen-equivalent units (FEU) by multiplying the DDU value by 2.

Area under the curve (AUC) outcome

AUC data was extracted as per the review protocol. However, not all studies reported this data. Where there was an AUC reported, there was often not a 95% confidence interval. All studies reported either likelihood ratios or sensitivity and specificity data and no studies reported only AUC data alone. The committee had a preference for likelihood ratios for decision-making. As there was sufficient data available for this, it was decided use of incomplete AUC data would not be required to support decision-making.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 20 and 21/12/2022. The following databases were searched: Medline, Medline in Process, Medline Epub ahead of Print, Embase (all Ovid platform) Cochrane Database of Systematic Reviews and Cochrane Central Register of Trials (Wiley platform) and Europe PMC to identify preprints. Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 11/01/2023. The following databases were searched: Medline, Medline in Process, Medline Epub ahead of Print, Embase, Econlit (all Ovid platform) and The International HTA database (the International Network of Agencies for Health Technology Assessment) Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 3296 references (see appendix B for the literature search strategy).

These 3296 references were screened at title and abstract level against the review protocol, with 3188 excluded at this level. 10% of references were screened separately by two reviewers. Discrepancies were resolved by discussion.

The full texts of 108 diagnostic studies were ordered for closer inspection. 16 of these studies met the criteria specified in the review protocol (appendix A). For a summary of the 16 included studies see Table 2 Summary of studies included in the diagnostic evidence.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the diagnostic evidence.

Table 2 Summary of studies included in the diagnostic evidence

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Bledsoe 2022 N= 3853 Study type: Retrospective cohort Study dates: March 2020 to February 2021	Setting: Emergency Department Location: USA	3583 adults with confirmed SARS-CoV-2 infection within the last 14 days. SARS-CoV-2 infection confirmed by PCR or antigen test	No information reported.	D-dimer test taken within 48hrs of arrival in the emergency department. Stago STA-LIATEST(T) D-DI Assay used. D-dimer threshold was standard 500 ng/mL cut-off	Chest CT, pulmonary perfusion, or pulmonary ventilation/perfusion scans that were conducted within 48hrs of arrival	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported. Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated)	Moderate
Elberts 2021 N= 238 Study type: Cross-sectional Study dates: December 2019 to December 2020	Setting: Emergency Department Location: USA	238 adults who underwent CTPA, D-dimer and COVID-19 testing in a single encounter. SARS-CoV-2 infection confirmed by positive test (test type not specified)	Reported not possible to generate Wells score due to retrospective nature of study.	D-dimer test taken as part of admission labs. 2 assays were used. Assay 1 used in 3 sites: STA Liatest D-dimer performed on a Stago platform with a threshold	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported. Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Low

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
				value of 0.50 mg/L fibrinogen equivalent units (FEU). Assay 2 used in 2 sites: HemosIL D-dimer HS, performed on ACL TOP 550 by Instrumentation Laboratory with a threshold value of 230 ng/mL D-dimer units (DDU).				
Revel 2022 N=781 Study type: Retrospective cohort Study dates: March 2020 to May 2020	Setting: Emergency department Location: France	781 adults with confirmed SARS-CoV-2 infection who had D-dimer and CTPA within 24hrs SARS-CoV-2 infection confirmed by RT-PCR.	No information reported.	D-dimer testing was measured using one of 3 locally available quantitative and highly sensitive D-dimer assays: ELISA VIDAS® D-Dimer	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported	Sensitivity Specificity LRs (calculated) AUC	High

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
				Exclusion™ II (bioMérieux SA) Automated latex-enhanced turbidimetric immunoassays: STA®-Liatest® D-Di Plus (Diagnostica Stago) HemosIL D-dimer HS500® (Instrumentation Laboratories) Thresholds used were standard 500ng/mL cut off and age-adjusted		Acute phase of COVID-19 illness.		
Silva 2021 N= 300	Setting: Emergency department Location: Portugal	300 adults who were SARS-COV-2 positive within previous 10 days	Wells score was retrospectively calculated.	D-dimer assay not further described. Thresholds used were standard	Computed tomography pulmonary angiography	Pre-Delta variant	Sensitivity Specificity LRs (calculated)	Low

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Study type: Cross-sectional Study dates: April 2020 to January 2021		and had a D-dimer result. SARS-CoV-2 infection confirmed by RT-PCR.	Patients were categorised as having low (<4.0 points), moderate (4.5–6.0points) or high(≥6.5 points) pretest probability of PE. Wells score <4 289 (96.3%) Wells score was used in diagnostic accuracy analysis.	500ng/mL cut off and age-adjusted. Wells score was retrospectively calculated: Pretest probability score using Wells: Low: <4 Moderate: 4.5-6 High: ≥6.5		Unvaccinated population COVID-19 severity: Not reported Acute phase of COVID-19 illness.	AUC	
Cerda 2020 N=92	Setting: Hospital Location: Spain	92 adults with confirmed SARS-CoV-2 infection,	Reported as not being validated in	D-dimer using an ACL TOP 750 System and ACL	Computed tomography	Pre-Delta variant	Sensitivity Specificity	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Study type: Cross-sectional Study dates: March 2020 to April 2020		admitted for COVID-19 pneumonia SARS-CoV-2 infection confirmed by RT-PCR and CT scan results typical of the disease.	the COVID-19 population.	TOP 500 (Instrumentation Laboratory, Germany). The threshold was set at 250 µg/L, except for those patients aged over 50 years for whom the recommended age adjusted cut-off (age × 10) was used	pulmonary angiography	Unvaccinated population COVID-19 severity: Not reported nut likely at least moderate due to COVID pneumonia. Acute phase of COVID-19 illness.	LRs (calculated) AUC	
Estrada N= 209 Study type: Cross-sectional Study dates: 2020 (not	Setting: Hospital Location: Columbia	209 adults with confirmed SARS-COV-2 infection with clinical suspicion of pulmonary embolism.	Wells score calculated retrospectively. Wells score ≤4 (unlikely) 159 (76.1%)	D-dimer by turbidimetric immunoassay. Threshold used was 499ng/mL	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity:	Sensitivity Specificity LRs AUC	High

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
further described)		SARS-CoV-2 infection confirmed by RT-PCR. Definition of clinical suspicion of PE not reported.	Wells score not included in accuracy analysis.			Moderate to critical Acute phase of COVID-19 illness.		
Leonard-Lorant 2020 N= 106 Study type: Cross-sectional Study dates: March 2020	Setting: Hospital Location: France	106 adults with confirmed SARS-CoV-2 infection who had CT examination. SARS-CoV-2 infection confirmed by RT-PCR or when RT-PCR results were negative, clinical judgement was used on CT images to confirm COVID-19.	Not reported	D-dimer levels were recorded for all patients who underwent pulmonary CT angiography. No D-dimer threshold reported	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Moderate
Logothetis 2021	Setting: Hospital	287 adults hospitalised with	Not reported	Plasma D-dimer concentrations	Computed tomography	Pre-Delta variant	Sensitivity	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
N=287 Study type: Cross-sectional Study dates: January 2020 to February 2021	Location: USA	COVID-19 who had clinical suspicion of pulmonary embolism. COVID-19 diagnostic criteria and clinical suspicion of PE not defined.		from an automated, standardised assay (expressed as FEU) Threshold used was 0.5 µg/mL	pulmonary angiography	Unvaccinated population COVID-19 severity: Not reported Acute phase of COVID-19 illness.	Specificity LRs (calculated) AUC	
Mouhat 2020 N=162 Study type: Cross-sectional Study dates: March 2020 to April 2020	Setting: Hospital Location: France	162 adults admitted with COVID-19 pneumonia who underwent CTPA for clinical signs of severity. SARS-CoV-2 infection confirmed by RT-PCR.	No information reported.	D-dimer was carried out on the same day as CTPA Threshold used not reported.	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
		Clinical signs of severity: oxygen saturation measured by pulse oximetry ⩽93% in room air, breathing rate of ⩾30 breaths min^{-1} or rapid clinical worsening.						
Nadeem 2021 N=193 Study type: Cross-sectional Study dates: November 2020 to January 2021	Setting: Hospital Location: UK	193 adults admitted with COVID-19 pneumonia who underwent CTPA for clinical suspicion of pulmonary embolism. SARS-CoV-2 infection confirmed by RT-PCR.	Wells score calculated retrospectiv ely. Wells score did not differ between PE+ and PE- groups. Reported that Wells score may not be	D-dimer was taken on admission. Latex agglutination assay was used to measure D-dimer. No pre-specified threshold was reported	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	High

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
		Clinical suspicion of PE not defined.	applicable to COVID-19. Wells score not included in accuracy analysis.					
Polo Friz 2020 N=41 Study type: Cross-sectional Study dates: April 2020	Setting: Hospital Location: Italy	41 adults with confirmed SARS-COV-2 infection who underwent CTPA. SARS-CoV-2 infection confirmed by RT-PCR.	Retrospectively calculated. Median Wells score (IQR) 2 (2-2) Not used in accuracy analysis.	D-dimer was measured by using HemosIL D-Dimer HS, a latex-enhanced turbidimetric immunoassay from Instrumentation Laboratory, on the fully automated coagulometer ACL TOP analyser Threshold used was <243 ng/mL.	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Quezada-Fejoo 2021 N= 50 Study type: Cross-sectional Study dates: March 2020 to May 2020	Setting: Hospital Location: Spain	Adults ages >75 years hospitalised with COVID-19 with a clinical suspicion of pulmonary embolism. SARS-CoV-2 infection confirmed by RT-PCR. Clinical probability of PE was assessed by the Wells and revised Geneva scores.	The Wells score was calculated to evaluate the probability of PE. Low risk was < 2 points, moderate risk from 2 to 6 points and high risk > 6 points. Wells score was included in accuracy analysis.	Peak D-dimer measure was used. Threshold used was 1mg/L	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported. Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated)	High
Raj 2021 N=109	Setting: Hospital Location: USA	109 adults who had imaging studies for pulmonary embolism within 90	Wells score was calculated retrospectiv ely.	D-dimers were obtained within seven days prior to the day of imaging for VTE	Computed tomography pulmonary angiography or V/Q scan	Pre-Delta variant	Sensitivity Specificity LRs (calculated)	High

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Study type: Retrospective cohort Study dates: 2020 (not further described)		days of COVID-19 illness SARS-CoV-2 infection confirmed by RT-PCR. Clinicians obtained imaging for VTE based on clinical judgment even when D-dimer or Wells scores were low	Wells score PE score <2 79(72.5%) Wells score not included in accuracy analysis with D-dimer.	with most values being drawn 1 to 3 days prior to being tested for VTE		Unvaccinated population COVID-19 severity: Not reported. Acute phase of COVID-19 illness but also included people up to 90 days from symptom onset. Data not disaggregated so numbers at 90 days not known.	AUC	
Ventura-Diaz 2020 N= 242	Setting: Hospital Location: Spain	242 adults with confirmed COVID-19 and suspected pulmonary embolism who receive CTPA.	No information reported.	Threshold for D-dimer was usual laboratory cut off of 500ng/ml.	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population	Sensitivity Specificity LRs (calculated) AUC	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
Study type: Cross-sectional Study dates: March 2020 to April 2020		SARS-CoV-2 infection confirmed by RT-PCR and CT scan results typical of the disease. Clinical suspicion of PE not defined.		No other information provided		COVID-19 severity: Not reported Acute phase of COVID-19 illness.		
Vivan 2022 N=697 Study type :Cross-sectional Study dates: March 2020 to May 2020	Setting: Hospital Location: Brazil	697 adults with confirmed symptomatic SARS-CoV-2 infection who had CTPA and D-dimer testing. SARS-CoV-2 infection confirmed by RT-PCR. Included people with symptoms of dyspnoea, feeling of heaviness/pressure in chest and	Reported as not able to utilise Wells score due to retrospective nature of study.	Serum D-dimer levels were evaluated using an automated particle-enhanced quantitative immunoturbidimetric assay (Innovance D-DIMER, Siemens Medical Solutions Diagnostics, Deerfield, IL, USA). Threshold was 0.3 microgram/mL or age adjusted	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Moderate

Study details	Setting/Location	Population	Wells score use	Index test	Reference standard	COVID-19 context information	Accuracy outcomes	Risk of bias
		oxygen saturation <95% of cyanosis.		[0.01 x (age -50 years. D-dimers were collected within 48hrs of CTPA.				
Whyte 2020 N= 214 Study type: Retrospective cohort Study dates: March 2020 to May 2020	Setting: Hospital Location: UK	214 adults admitted for COVID-19 with suspected pulmonary embolism. SARS-CoV-2 infection confirmed by RT-PCR. Clinical suspicion of PE not defined.	Retrospectively calculated. Wells score <4 (unlikely) 158 (73.8%) Not used in accuracy analysis.	D-dimer was measured by a latex photometric immunoassay, with STA-Liatest. Threshold used was 500 ng/mL	Computed tomography pulmonary angiography	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	High

1 See appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Table 3: D-dimer tests with standard cut-offs for pulmonary embolism in COVID-19

No of studies (sample size)	Diagnostic accuracy			Quality	Interpretation of effect
	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)		
Wells score (low to moderate risk; <6) plus D-dimer threshold 500ng/ml					
1 (n=300) Silva 2021	95.7 (85.2 to 99.5)	8.3 (5.19 to 12.4)	LR+ 1.04 (0.97 to 1.12)	Moderate	Slight increase in probability of pulmonary embolism (95% CI crosses 1).
			LR- 0.53 (0.13 to 2.17)	Low	Slight decrease in probability of pulmonary embolism (95% CI crosses 1).
D-dimer with a threshold of 500ng/ml (no Wells score)					
9 (n=6245)	96 (93 to 98)	14 (8 to 24)	LR+ 1.13 (1.04 to 1.26)	Very low	Slight increase in probability of pulmonary embolism. (95% CI within this range).
			LR- 0.28 (0.11 to 0.57)	Very low	Moderate decrease in probability of pulmonary embolism (95% CI ranges from slight to large decrease).
Age-adjusted D-dimer (no Wells score)					
2 (n=606)	90.5 (79.1 to 96)	27.4 (14.9 to 44.7)	LR+ 1.264 (1.007 to 1.58)	Very low	Slight increase in probability of pulmonary embolism (95% CI within this range).

			LR- 0.317 (0.135 to 0.743)	Very low	Moderate decrease in probability of pulmonary embolism (95% CI ranges from slight to large decrease).

Table 4: D-dimer tests with higher cut-offs for pulmonary embolism in COVID-19

No of studies (sample size)	Diagnostic accuracy			Quality	Interpretation of effect
	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)		
Wells score <2.5 plus a D-dimer threshold of 4300ng/ml					
1 (n=50) Quezada-Feijoo 2021	35.3 (17.3 to 58.7)	97 (84.7 to 99.5)	LR+ 11.65 (1.52 to 89.09)	Very low	Very large increase in probability of pulmonary embolism (95% CI ranges from slight to very large increase).
			LR- 0.67 (0.47 to 0.95)	Very low	Slight decrease in probability of pulmonary embolism (95% CI ranges from slight to moderate decrease).
D-dimer threshold of 632 ng/ml (no Wells score)					
1 (n= 92) Cerda 2020	89.7 (73.6 to 96.4)	52.4 (40.3 to 64.2)	LR+ 1.88 (1.41 to 2.51)	Low	Slight increase in probability of pulmonary embolism (95% CI ranges from slight to moderate increase).
			LR- 0.20 (0.07 to 0.59)	Low	Large decrease in probability of pulmonary embolism (95% CI ranges from slight to moderate decrease).
D-dimer threshold of 1000ng/ml (no Wells score)					

1 (n=50) Quezada-Feijoo 2021	97.2 (67.8 to 99.8)	30.9 (17.8 to 48)	LR+ 1.41 (1.11 to 1.78)	Low	Slight increase in probability of pulmonary embolism (95% CI within this range).
			LR- 0.09 (0.01 to 1.45)	Very low	Very large decrease in probability of pulmonary embolism (95% CI crosses 1).
D-dimer threshold of 1500ng/ml (no Wells score)					
1 (n=109) Raj 2021	80.8 (62.1 to 91.5)	85.5 (76.4 to 91.5)	LR+ 5.59 (3.20 to 9.74)	Low	Large increase in probability of pulmonary embolism (95% CI ranges from large to very large increase).
			LR- 0.22 (0.10 to 0.50)	Low	Moderate decrease in probability of pulmonary embolism (95% CI ranges from slight to large decrease).
D-dimer threshold of 2000ng/ml (no Wells score)					
2 (n=4634)	74 (64 to 82)	78 (69 to 86)	LR+ 3.52 (2.70 to 4.57)	Very low	Moderate increase in probability of pulmonary embolism (95% CI within this range).
			LR- 0.34 (0.27 to 0.43)	Low	Moderate decrease in probability of pulmonary embolism (95% CI within this range).
D-dimer threshold of 2281 ng/ml (no Wells score)					
1 (n=209) Estrada 2022	60.0 (53.4 to 66.6)	76.9 (70.9 to 82.4)	LR+2.57 (2.1 to 3.14)	Low	Moderate increase in probability of pulmonary embolism (95% CI within this range).
			LR-0.52 (0.42 to 0.65)	Very low	Slight decrease in probability of pulmonary embolism (95% CI ranges from slight to moderate decrease).

D-dimer threshold of 2454 ng/ml (no Wells score)					
1 (n= 41) Polo Friz 2020	63 (24 to 91)	73 (54 to 87)	LR+ 2.29 (1.06 to 4.97)	Very low	Moderate increase in probability of pulmonary embolism (95% CI ranges slight to moderate increase).
			LR- 0.52 (0.21 to 1.29)	Very low	Slight decrease in probability of pulmonary embolism (95% crosses 1).
D-dimer threshold of 2495 ng/ml (no Wells score)					
1 (n=193) Nadeem 2021	98.5 (80.4 to 99.9)	90.4 (84.8 to 94.1)	LR+ 10.23 (6.37 to 16.46)	Low	Very large increase in probability of pulmonary embolism (95% CI ranges from large to very large increase).
			LR- 0.02 (0.001 to 0.26)	Low	Very large decrease in probability of pulmonary embolism (95% CI ranges from moderate to very large decrease).
D-dimer threshold of 2590 ng/ml (no Wells score)					
1 (n=162) Mouhat 2020	83.3 (68.6 to 93)	83.8 (3.8 to 91.1)	LR+ 5.22 (3.39 to 8.04)	Moderate	Large increase in probability of pulmonary embolism (95% CI ranges from moderate to large increase).
			LR- 0.19 (0.10 to 0.38)	Moderate	Large decrease in probability of pulmonary embolism (95% CI ranges from moderate to large decrease).
D-dimer threshold of 2660 ng/ml (no Wells score)					
1 (n=106)	99 (80 to 100)	67.6 (56.3 to 77.1)	LR+ 3.02 (2.173 to 4.184)	Low	Moderate increase in probability of pulmonary embolism (95% CI within this range).

Leonard-Lorant 2020			LR- 0.023 (0.001 to 0.354)	Low	Very large decrease in probability of pulmonary embolism (95% CI ranges from moderate to very large decrease).
D-dimer threshold of 2903 ng/ml (no Wells score)					
1 (n=242) Ventura-Diaz 2020	80.8 (70.3 to 88.2)	59.2 (51.6 to 66.3)	LR+ 1.98 (1.6 to 2.45)	Very low	Slight increase in probability of pulmonary embolism (95% CI ranges from slight to moderate increase).
			LR- 0.32 (0.2 to 0.53)	Very low	Moderate decrease in probability of pulmonary embolism (95% CI ranges from slight to moderate decrease).
D-dimer threshold of 4800 ng/ml (no Wells score)					
1 (n=214) Whyte 2020	75.0 (64.5 to 83.2)	78.4 (70.6 to 84.5)	LR+ 3.47 (2.45 to 4.9)	Low	Moderate increase in probability of pulmonary embolism (95% CI within this range).
			LR- 0.32 (0.22 to 0.47)	Low	Moderate decrease in probability of pulmonary embolism (95% CI within this range).

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to both of the questions in this guideline update (see Appendix B). This search retrieved 90 studies. Based on title and abstract screening, all studies were excluded.

1.1.7.2 Excluded studies

No studies were screened at full text.

1.1.8 Summary of included economic evidence

No studies were identified.

1.1.9 Economic model

This area was not prioritised for economic evaluation.

Details regarding the estimation of testing outcomes and economic consequences of false positive tests are provided in appendix I.

1.1.11 Evidence statements

D-dimer tests with standard thresholds for pulmonary embolism in COVID-19

Wells score <6 and D-dimer threshold 500ng/ml

- Evidence suggests that a Wells score<6 and a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism (LR+ 1.04 [0.97 to 1.12]). (Moderate quality evidence from 1 cross-sectional study; n=300).

- Evidence suggests that a Wells score<6 and a negative D-dimer result indicates a slight decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.53 [0.13 to 2.17]). (Low quality evidence from 1 cross-sectional study; n=300).

D-dimer threshold 500ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism (LR+ 1.13 [1.04 to 1.26]). (Very low-quality evidence from 9 retrospective studies; n=6245).

- Evidence suggests that a negative D-dimer result indicates moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism (LR- 0.28 [0.11 to 0.57]). (Very low-quality evidence from 9 retrospective studies; n=6245).

Age-adjusted D-dimer threshold (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism (LR+ 1.264 [1.007 to 1.586]. (Very low-quality evidence from 2 retrospective studies; n=606).
- Evidence suggests that a negative D-dimer result indicates a slight to moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.317 [0.135 to 0.743] ((Very low-quality evidence from 2 retrospective studies; n=606).

D-dimer tests with higher cut-offs for pulmonary embolism in COVID-19

Wells score <2.5 plus a D-dimer threshold of 4300ng/ml

- Evidence suggests that a Wells score <2.5 and positive D-dimer result indicates a very large increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 11.65 [1.52 to 89.09]). (Very low-quality evidence from 1 cross-sectional study; n=50).
- Evidence suggests that a Wells score <2.5 and negative D-dimer result indicates slight decrease in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.67 [0.47 to 0.95]). (Very-low quality evidence from 1 cross-sectional study; n=50).

D-dimer threshold of 632 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 1.88 [1.41 to 2.51]). (Low quality evidence from 1 cross-sectional study; n=92).
- Evidence suggests that a negative D-dimer result indicates a large decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.20 [0.07 to 0.59]). (Low quality evidence from 1 cross-sectional study; n=92).

D-dimer threshold of 1000ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 1.41 [1.11 to 1.78]). (Low quality evidence from 1 cross-sectional study; n=50).
- Evidence suggests that a negative D-dimer result indicates a very large decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.09 [0.01 to 1.45]). (Very low-quality evidence from 1 cross-sectional study; n=50).

D-dimer threshold of 1500ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a large increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 5.59 [3.20 to 9.74]). (Low quality evidence from 1 retrospective cohort study; n=109).
- Evidence suggests that a negative D-dimer result indicates a moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.22 [0.10 to 0.50]). (Low quality evidence from 1 retrospective cohort study; n=109).

D-dimer threshold of 2000ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 3.52 [2.70 to 4.57]). (Very-low quality evidence from 2 retrospective cohort studies; n=4634).
- Evidence suggests that a negative D-dimer result indicates a moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.34 [0.27 to 0.43] (Low quality evidence from 2 retrospective cohort studies; n=4634).

D-dimer threshold of 2281 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 2.57 [2.1 to 3.14]). (Low quality evidence from 1 cross-sectional study; n=209).
- Evidence suggests that a negative D-dimer result indicates a slight decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.52 [0.42 to 0.65]). (Very-low quality evidence from 1 cross-sectional study; n=209).

D-dimer threshold of 2454 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 2.29 [1.06 to 4.97]). (Very-low quality evidence from 1 cross-sectional study; n=41).
- Evidence suggests that a negative D-dimer result indicates a slight decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.52 [0.21 to 1.29]). (Very-low quality evidence from 1 cross-sectional study; n=41).

D-dimer threshold of 2495 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a very large increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 10.23 [6.37to 16.46]). (Low quality evidence from 1 cross-sectional study; n=193).
- Evidence suggests that a negative D-dimer result indicates a very large decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.02 [0.001 to 0.26]). (Low quality evidence from 1 cross-sectional study; n=193).

D-dimer threshold of 2590 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a large increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 5.22 [3.39 to 8.04]). (Moderate quality evidence from 1 cross-sectional study; n=162).
- Evidence suggests that a negative D-dimer result indicates a large decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.19 [0.10 to 0.38]). (Moderate quality evidence from 1 cross-sectional study; n=162).

D-dimer threshold of 2660 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 3.02 [2.173 to 4.184]). (Low quality evidence from 1 cross-sectional study; n=106).
- Evidence suggests that a negative D-dimer result indicates a very large decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.023 [0.001 to 0.354]). (Low-quality evidence from 1 cross-sectional study; n=106).

D-dimer threshold of 2903 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 1.98 [1.6 to 2.45]). (Very low-quality evidence from 1 cross-sectional study; n=242).
- Evidence suggests that a negative D-dimer result indicates a moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.32 [0.2 to 0.53]). (Very low-quality evidence from 1 cross-sectional study; n=242).

D-dimer threshold of 4800 ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in the probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR+ 3.47 [2.45 to 4.9]). (Low-quality evidence from 1 retrospective cohort study; n=214).
- Evidence suggests that a negative D-dimer result indicates a moderate decrease in probability that a person with COVID-19 and suspected pulmonary embolism has pulmonary embolism. (LR- 0.32 [0.22 to 0.47]). (Low-quality evidence from 1 retrospective cohort study; n=214).

1.1.12 The committee's discussion and interpretation of the evidence

The committee discussion of the review on diagnosing pulmonary embolism in people with COVID-19 is included in the discussion of the review on diagnosing deep vein thrombosis in COVID-19. See section 2.1.12.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6, 1.1.7, 1.1.11, 1.1.20 and 1.1.21.

1.1.14 References – included studies

1.1.14.1 Diagnostic evidence

Bledsoe, Joseph R, Knox, Daniel, Peltan, Ithan D et al. (2022) D-dimer Thresholds to Exclude Pulmonary Embolism among COVID-19 Patients in the Emergency Department: Derivation with Independent Validation. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 28: 10760296221117997

Cerda, Pau, Ribas, Jesus, Iriarte, Adriana et al. (2020) Blood test dynamics in hospitalized COVID-19 patients: Potential utility of D-dimer for pulmonary embolism diagnosis. PloS one 15(12): e0243533

Cho, Edward S, McClelland, Paul H, Cheng, Olivia et al. (2021) Utility of d-dimer for diagnosis of deep vein thrombosis in coronavirus disease-19 infection. Journal of vascular surgery. Venous and lymphatic disorders 9(1): 47-53

Elberts, Samuel J, Bateman, Ryan, Koutsoubis, Alexandra et al. (2021) The impact of COVID-19 on the sensitivity of D-dimer for pulmonary embolism. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 28(10): 1142-1149

Estrada, Víctor Hugo Nieto, Valle, Anacaona Martínez Del, Moreno, Albert Alexander Valencia et al. (2022) Rethinking D-dimer's role in the diagnosis of pulmonary thromboembolism in patients with COVID-19: analysis of a diagnostic test study.

Gibson, Cameron J, Alqunaibit, Dalia, Smith, Kira E et al. (2020) Probative Value of the D-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome. Critical care medicine 48(12): e1322-e1326

Leonard-Lorant, Ian, Delabranche, Xavier, Severac, Francois et al. (2020) Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. Radiology 296(3): e189-e191

Logothetis, Constantine N, Weppelmann, Thomas A, Jordan, Aryanna et al. (2021) D-Dimer Testing for the Exclusion of Pulmonary Embolism Among Hospitalized Patients With COVID-19. JAMA network open 4(10): e2128802

Mouhat, Basile, Besutti, Matthieu, Bouiller, Kevin et al. (2020) Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. The European respiratory journal 56(4)

Nadeem, Iftikhar, Anwar, Asad, Jordon, Louise et al. (2021) Relationship of D-dimer and prediction of pulmonary embolism in hospitalized COVID-19 patients: a multicenter study. Future microbiology 16: 863-870

Polo Friz, Hernan, Gelfi, Elia, Orenti, Annalisa et al. (2021) Acute pulmonary embolism in patients presenting pulmonary deterioration after hospitalisation for non-critical COVID-19. Internal medicine journal 51(8): 1236-1242

Quezada-Feijoo, M., Ramos, M., Lozano-Montoya, I. et al. (2021) Elderly population with COVID-19 and the accuracy of clinical scales and d-dimer for pulmonary embolism: The OCTA-COVID study. Journal of Clinical Medicine 10(22): 5433

Raj K, Chandna S, Doukas SG et al. (2021) Combined Use of Wells Scores and D-dimer Levels for the Diagnosis of Deep Vein Thrombosis and Pulmonary Embolism in COVID-19: A Retrospective Cohort Study. Cureus 13(9): e17687

Revel, Marie-Pierre, Beeker, Nathanael, Porcher, Raphael et al. (2022) What level of D-dimers can safely exclude pulmonary embolism in COVID-19 patients presenting to the emergency department?. European radiology 32(4): 2704-2712

Silva, Beatriz Valente, Jorge, Claudia, Placido, Rui et al. (2021) Pulmonary embolism and COVID-19: A comparative analysis of different diagnostic models performance. The American journal of emergency medicine 50: 526-531

Trigonis, Russell A, Holt, Daniel B, Yuan, Rebecca et al. (2020) Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. Critical care medicine 48(9): e805-e808

Ventura-Diaz, Sofia, Quintana-Perez, Juan V, Gil-Boronat, Almudena et al. (2020) A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study. Emergency radiology 27(6): 679-689

Whyte, Martin B, Kelly, Philip A, Gonzalez, Elisa et al. (2020) Pulmonary embolism in hospitalised patients with COVID-19. Thrombosis research 195: 95-99

Vivan, M.A., Rigatti, B., da Cunha, S.V. et al. (2022) Pulmonary embolism in patients with COVID-19 and D-dimer diagnostic value: A retrospective study. Brazilian Journal of Infectious Diseases 26(6): 102702

2 Diagnosis of deep vein thrombosis in COVID-19

2.1 Review question

In people with COVID-19 and suspected DVT, can we safely rule out the need for further imaging based on a combination of clinical probability score and D-dimer assay?

2.1.1 Introduction

This is an update of NG158: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing focusing on diagnosing VTE in people with COVID-19. NG158 currently recommends that D-dimer testing should be used to rule out the need for imaging in someone with suspected DVT with a Wells score that suggests DVT is unlikely. D-dimer testing thresholds for ruling out imaging are specific to the type of D-dimer test used and can be fixed or age adjusted. This adjustment accounts for D-dimer levels increasing with age. The surveillance review conducted in 2022 highlighted that D-dimer levels can be elevated in people with COVID-19 in the blood due to inflammation. There may also be a higher risk of blood clots associated with COVID-19. Therefore, guidance is needed on whether any modifications are required for the use of the Wells score for pre-test probability and D-dimers in the diagnosis of DVT in people with COVID-19. These modifications may include adjusting D-dimer threshold levels for people with COVID-19 whilst minimising the risk of missed DVT diagnoses.

2.1.2 Summary of the protocol

Table 5: PICOS inclusion criteria

Population	Adults with clinically suspected or confirmed COVID-19, or recent history of COVID-19 (within the past 6 months), and suspected DVT
Index test	D-dimer test (age-adjusted or fixed test threshold) alone or in combination with a DVT Wells score
Reference standard	Compression ultrasound, venography, lower limb MRV scan, lower limb CT venogram, VTE event during 3 months of follow-up (for people discharged without imaging because they are considered low risk)

Outcomes	Diagnostic accuracy metrics: sensitivity/specificity, positive and negative likelihood ratios, area under the curve
Study type	Diagnostic accuracy cross-sectional studies and cohort studies.

For the full protocol see appendix A.

2.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Methods specific to this review:

Use of pre-print (non-peer reviewed) publications

The search was expanded to include pre-print publication servers. This is because many authors chose to release manuscripts on pre-print servers to enable rapid dissemination of information during the COVID-19 pandemic.

Diagnostic accuracy measures

The committee chose likelihood ratios as the diagnostic accuracy measures to inform decision-making so GRADE was applied to these measures. The GRADE tables include measures of sensitivity and specificity which were presented to the committee to help with understanding the impact on false negative and false positive rates.

Where meta-analysis was not conducted, the following data was extracted where possible:

Likelihood ratios

- likelihood ratios and their corresponding 95% CI intervals were extracted from the individual studies where reported.
- likelihood ratios and their corresponding 95% CI intervals were calculated by the reviewer from 2x2 data where not reported in the study.

Sensitivity and specificity

- sensitivity and specificity and their corresponding 95% CI intervals were extracted from the individual studies where reported.
- sensitivity and specificity and their corresponding 95% CI intervals were calculated by the reviewer from 2x2 data where not reported in the study.

D-dimer measures

- Values of D-dimer were converted to units of ng/mL as this was the most reported unit.
- Where studies report D-dimer values as D-dimer units (DDU), these were converted to fibrinogen-equivalent units (FEU) by multiplying the DDU value by 2.

Area under the curve (AUC) outcome

AUC data was extracted as per the review protocol. However, not all studies reported this data. Where there was an AUC reported, there was often not a 95% confidence interval. All studies reported either likelihood ratios or sensitivity and specificity data and no studies reported only AUC data alone. The committee had a preference for likelihood ratios for decision-making. As there was sufficient data available for this, it was decided use of incomplete AUC data would not be required to support decision-making

2.1.3.1 Search methods

See section 1.1.3.1 for details.

2.1.4 Diagnostic evidence

2.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 3296 references (see appendix B for the literature search strategy).

These 3296 references were screened at title and abstract level against the review protocol, with 3188 excluded at this level. 10% of references were screened separately by two reviewers. Discrepancies were resolved by discussion.

The full texts of 108 diagnostic studies were ordered for closer inspection. Of these studies, 4 met the criteria specified in the review protocol (appendix A). For a summary of the 4 included studies see Table 6 Summary of studies included in the diagnostic evidence.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

2.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

2.1.5 Summary of studies included in the diagnostic evidence.

Table 6 Summary of studies included in the diagnostic evidence

Study details	Setting/Location	Population	Use of Wells score	Index test	Reference standard	COVID-19 context information	Accuracy measures	Risk of bias
Cho 2020 N= 158 Study type: Cross-sectional Study dates: March 2020 to May 2020	Setting: Hospital Location: USA	158 adults with confirmed COVID-19 who had D-dimer test and venous duplex ultrasound examinations. SARS-CoV-2 infection confirmed by RT-PCR. Those considered high risk for DVT based on clinical criteria (no further information reported)	Reported that Wells score has not been validated in COVID-19. Wells score retrospectively calculated. Wells score ≥ 2 (Likely) 56 (35.4%) Wells score not included in accuracy analysis.	Acute-phase D-dimer values, defined as the highest D-dimer level before obtaining venous duplex ultrasound examination, were used to compare with the presence of confirmed DVT. Threshold was the conventional reference range of 230ng/mL; or less (DDU)	Venous duplex ultrasound	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe. Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated) AUC	Moderate
Gibson 2020 N= 72	Setting: Hospital Location: USA	72 intubated adults with critical COVID-19	Wells score retrospectively calculated.	D-dimer assays were performed by clot curve analysis on an ACL TOP 700	Lower extremity duplex ultrasound.	Pre-Delta variant	Sensitivity Specificity LRs (calculated)	High

Study details	Setting/Location	Population	Use of Wells score	Index test	Reference standard	COVID-19 context information	Accuracy measures	Risk of bias
Study type: Retrospective cohort Study dates: April 2020		SARS-CoV-2 infection confirmed by RT-PCR.	Wells score place all participants at increased risk of DVT. Wells score not included in accuracy analysis.	Laboratory Automation System (Instrumentation Laboratory, Bedford, MA).		Unvaccinated population COVID-19 severity: Critical. Acute phase of COVID-19 illness.	AUC	
Raj 2021 N=106 Study type: Retrospective cohort Study dates: 2020 (Not further described)	Setting: Hospital Location: USA	106 adults who had imaging studies for DVT within 90 days of COVID-19 illness SARS-CoV-2 infection confirmed by RT-PCR. Clinicians obtained imaging for VTE based on clinical	Wells score was calculated retrospectively. Wells score DVT score <2 66 (62.2%) Wells score not included in accuracy analysis with D-dimer.	D-dimers were obtained within seven days prior to the day of imaging for VTE with most values being drawn 1 to 3 days prior to being tested for VTE	Lower extremity duplex ultrasound.	Pre-Delta variant Unvaccinated population COVID-19 severity: Not reported Acute phase of COVID-19 illness but included people up to 90 days from onset of illness.	Sensitivity Specificity LRs (calculated) AUC	High

Study details	Setting/Location	Population	Use of Wells score	Index test	Reference standard	COVID-19 context information	Accuracy measures	Risk of bias
		judgment even when D-dimer or Wells scores were low						
Trigonis 2020 N= 45 Study type: Cross-sectional Study dates: April 2020 to January 2021	Setting: Hospital Location: USA	45 adults hospitalised with confirmed SARS-CoV-2 infection requiring intubation and mechanical ventilation. SARS-CoV-2 confirmation criteria not reported.	No information reported.	D-dimer values were recorded as the value closest to the date of ultrasound as well as the overall maximum value during the hospitalisation. A range of D-dimer thresholds were examined. (1000ngmLl to 10000 ng/mL)	Ultrasound (not further described)	Pre-Delta variant Unvaccinated population COVID-19 severity: Severe to critical Acute phase of COVID-19 illness.	Sensitivity Specificity LRs (calculated)	High

1 See appendix D for full evidence tables.

2 ### 2.1.6 Summary of the diagnostic evidence

3 **Table 7: D-dimer tests for deep vein thrombosis in COVID-19**

	Diagnostic accuracy	Quality	Interpretation of effect

No of studies (sample size)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)		
D-dimer threshold of 500ng/ml (no Wells score)					
1 (n=106) Raj 2021	94.3 (81.4 to 98.4)	29.6 (20.2 to 41)	LR+ 1.34 (1.13 to 1.59)	Low	Slight increase in probability of deep vein thrombosis (95% CI within this range).
			LR- 0.19 (0.05 to 0.78)	Very low	Large decrease in probability of deep vein thrombosis (95% CI ranges from slight to very large decrease).
D-dimer threshold of 1500ng/ml (no Wells score)					
1 (n=106) Raj 2021	74.3 (57.9 to 85.8)	77.5 (66.5 to 85.6)	LR+ 3.3 (2.05 to 5.29)	Low	Moderate increase in probability of deep vein thrombosis (95% CI ranges from moderate to large increase).
			LR- 0.33 (0.19 to 0.59)	Very low	Moderate decrease in probability of deep vein thrombosis (95% CI slight to large decrease).
D-dimer threshold of 2000ng/ml (no Wells score)					
1 (n=106) Trigonis 2020	94.7 (75.4 to 99.1)	46.2 (28.8 to 64.5)	LR+ 1.76 (1.21 to 2.55)	Very low	Slight increase in probability of deep vein thrombosis (95% CI ranges from slight to moderate increase).
			LR- 0.11 (0.02 to 0.8)	Very low	Large decrease in probability of deep vein thrombosis (95% CI ranges from large to very large decrease).
D-dimer threshold of 3000ng/ml (no Wells score)					
1 (n=72) Gibson 2020	96.2 (59.7 to 99.8)	51.6 (39.3 to 63.8)	LR+ 1.99 (1.50 to 2.63)	Very low	Slight increase in probability of deep vein thrombosis (95% CI ranges from slight to moderate increase).

			LR- 0.07 (0.01 to 1.14)	Very low	Very large decrease in probability of deep vein thrombosis (95% CI crosses 1).
D-dimer threshold of 6494ng/ml (no Wells score)					
1 (n=158) Cho 2020	80.8 (68.1 to 89.2)	68.9 (59.5 to 76.9)	LR+ 2.59 (1.9 to 3.55)	Very low	Moderate increase in probability of deep vein thrombosis (95% CI ranges from slight to moderate increase).
			LR- 0.28 (0.16 to 0.49)	Low	Moderate decrease in probability of deep vein thrombosis (95% CI ranges from moderate to large decrease)..

See appendix F for full GRADE tables.

2.1.7 Economic evidence

2.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to both of the questions in this guideline update (see Appendix B: Literature search strategies). This search retrieved 90 studies. Based on title and abstract screening, all studies were excluded.

2.1.7.2 Excluded studies

No studies were screened at full text.

2.1.8 Summary of included economic evidence

No studies were identified.

2.1.9 Economic model

This area was not prioritised for economic evaluation.

Details regarding the estimation of testing outcomes and economic consequences of false positive tests are provided in Appendix I: Health economic model.

2.1.11 Evidence statements

D-dimer tests for deep vein thrombosis in COVID-19

D-dimer threshold of 500ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and deep vein thrombosis has deep vein thrombosis (LR+ 1.34 [1.13 to 1.59]). (Low quality evidence from 1 retrospective cohort study; n=106).

- Evidence suggests that a negative D-dimer result indicates large decrease in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR- 0.19 [0.05 to 0.78]). (Very low-quality evidence from 1 retrospective cohort study; n=106).

D-dimer threshold of 1500ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR+ 3.3 [2.05 to 5.29]). (Low quality evidence from 1 retrospective cohort study; n=106).

- Evidence suggests that a negative D-dimer result indicates moderate decrease in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR- 0.33 [0.19 to 0.59]). (Very low-quality evidence from 1 retrospective cohort study; n=106).

D-dimer threshold of 2000ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR+ 1.76 [1.21 to 2.55]). (Very low-quality evidence from 1 cross-sectional study; n=106).

- Evidence suggests that a negative D-dimer result indicates large decrease in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR- 0.11 [0.02 to 0.8]). (Very low-quality evidence from 1 cross-sectional study; n=106).

D-dimer threshold of 3000ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a slight increase in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR+ 1.99 [1.50 to 2.63]). (Very low-quality evidence from 1 retrospective cohort study; n=72).

- Evidence suggests that a negative D-dimer result indicates very large decrease in probability that a person with COVID-19 and deep vein thrombosis has deep vein thrombosis. (LR- 0.07 [0.01 to 1.14]). (Very low-quality evidence from 1 retrospective cohort study; n=72).

D-dimer threshold of 6494ng/ml (no Wells score)

- Evidence suggests that a positive D-dimer result indicates a moderate increase in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR+ 2.59 [1.9 to 3.55). (Very low-quality evidence from 1 retrospective cohort study; n=158).

- Evidence suggests that a negative D-dimer result indicates moderate decrease in probability that a person with COVID-19 and suspected deep vein thrombosis has deep vein thrombosis (LR- 0.28 [0.16 to 0.49]). (Low-quality evidence from 1 retrospective cohort study; n=158).

2.1.12 The committee's discussion and interpretation of the evidence

2.1.12.1. The outcomes that matter most

Pulmonary embolism and deep vein thrombosis

The committee discussed the existing diagnostic pathway relative to the COVID-19 population, considering the impact of true positive, false positive, true negative and false negative D-dimer results on patients. Those with true positive D-dimer tests undergo further imaging which is usually computed tomography pulmonary angiography (CTPA) to confirm PE diagnosis or ultrasound for DVT. Where diagnosis is confirmed, appropriate anticoagulation is initiated or continued. Those with false positive D-dimer tests will undergo imaging that may be unnecessary. This could lead to increased anxiety in the patient as well as additional healthcare costs. There may also be clinical consequences of imaging, including increased radiation and its potential impact on kidney function. People with false positive results may also be given unnecessary interim therapeutic anticoagulation whilst awaiting imaging which may carry a risk of bleeding. However, the committee noted that people in hospital for moderate COVID-19 will likely be receiving therapeutic doses of heparins for VTE prevention (as recommended in NICE NG191 COVID-19 rapid guideline: managing COVID-19), so in this population a false positive D-dimer result will not cause unnecessary anticoagulation. People with true negative D-dimer results are correctly discharged and reassured that they do not have a PE or DVT. People with false negative results may be incorrectly discharged without treatment and a risk of disease progression and complications, including death. The committee further discussed lived experiences of the consequences from having a false negative result. From the patient perspective, this includes long-term anxiety due to requiring additional appointments or hospitalisations that could have been prevented. This in turn can lead to loss of trust in healthcare providers and feeling that their concerns are not being taken seriously, resulting in a long-term impact on future healthcare interactions. From the clinician perspective, there are concerns about wrongly reassuring patients who go on to develop complications that can potentially impact on trust and reputation.

When considering the relative importance of false negatives and false positives, the committee were most concerned with keeping the false negative rates to a minimum. This means that the sensitivity of the D-dimer test is important. The committee discussed that the elevated D-dimers in people with COVID-19 may lead to more false positive D-dimer results which lowers the specificity of the test. However, on balance the committee still valued the sensitivity (and negative likelihood ratios) of a test over specificity (and positive likelihood ratios) as it was most important to minimise the number of people with COVID-19 who go on to have an undiagnosed VTE. This reflects current practice whereby negative D-dimers are used to exclude VTE due to D-dimer being both an inflammatory and thrombotic marker.

2.1.12.2 The quality of the evidence

Pulmonary embolism and deep vein thrombosis

The evidence measuring the accuracy of D-dimer tests for diagnosing PE or DVT in people with COVID-19 was of very low to moderate quality and consisted of cross-sectional and retrospective studies. Due to the retrospective nature of the studies, there were several uncertainties around whether the population selected in the evidence base was representative of the population this guidance applies to. For example, the evidence base included only those that had received imaging but it was difficult to ascertain from the retrospective data the reason behind why individuals had received imaging. Studies rarely included a definition of clinical suspicion of PE or DVT. It is possible that the population from the evidence is limited to those with high clinical suspicion as these people would usually receive imaging. However, where pre-test probability was retrospectively calculated using the Wells PE score, a large proportion of those who received imaging were low to moderate risk for PE. One of the main reasons for downgrading for risk of bias was due to uncertainty around whether interpretation of D-dimers and the reference standards were made independently of each other. Most of the studies focused on diagnosing DVT or PE, not both. It is therefore possible that some of participants who had negative imaging could have had a DVT or PE but this would not have been investigated in the study. As people with COVID-19 may have elevated D-dimers even in the absence of DVT or PE, some of the studies used a higher threshold for defining a D-dimer result as positive than in people without COVID-19, in order to reduce the number of false positive results and to increase the specificity of the test. However, these were not validated thresholds and often came from relatively small studies. The committee were not confident that these thresholds could be used as part of the decision-making due to the high uncertainty surrounding them and lack of validation.

Whilst the evidence met the criteria in the protocol and was not downgraded for indirectness, the committee considered the evidence in the context of COVID-19 in England in early 2023. All the evidence was carried out early in the pandemic (March to May 2020). This means that the population would have most likely had COVID-19 attributed to pre-Delta variants, been unvaccinated and therefore likely to have had moderate to critical illness. This is vastly different from the population 3 years later following the emergence of the Omicron variant and its subvariants which is deemed to be a milder illness. Much of the population now have been vaccinated or have had COVID-19. The committee agreed that in practice, there are fewer people being admitted to hospital for COVID-19 and are therefore fewer instances of COVID-19 related VTE. The committee also noted that as the disease mechanism of COVID-19 is better understood, symptoms similar to PE in COVID-19 may instead be symptoms of immunothrombosis linked with the inflammatory response attributed to COVID-19. However, the committee discussed that immunothrombosis is also seen less now due to the introduction of corticosteroids and IL-6 inhibitors to the COVID-19 treatment pathway. Even though the rates of PE in COVID-19 are much lower now compared with the populations included in the studies, and there is potential alternative diagnosis of immunothrombosis, the committee agreed that there should still be high suspicion of PE where there are signs of rapid deterioration and hypoxia in people with COVID-19.

The reference standard used for pulmonary embolism in the studies was computed tomography pulmonary angiography (CTPA). The committee acknowledged that at the time the studies were conducted, CTPA would have been the most likely imaging used for diagnosing PE. However, they noted that CTPA as a reference standard would not be suitable for identifying immunothrombosis in capillaries. The committee considered this important in terms of managing people with COVID-19 who require respiratory support but who have negative CTPA for pulmonary embolism because they may still require anticoagulation.

2.1.12.3 Benefits and harms

The committee explored how clinically useful findings were by applying minimal important clinical differences (MID) to the likelihood ratios. For a positive likelihood ratio the MID was 2.0 and for negative likelihood ratio 0.5 with both using 1 (which is the null value for ratios) as the second value. Point estimate values which fell within these MIDs were described as not meaningfully altering the likelihood of PE or DVT as they gave a slight increase or decrease in the likelihood of having a PE or DVT and were thought to be non-clinically significant by the committee. Likelihood ratios where the 95% confidence interval crossed 1 were also described as not meaningfully altering the likelihood of PE or DVT.

Pulmonary embolism

The evidence suggested that a Wells score <6 (low to moderate risk of PE) in combination with the usual D-dimer threshold of 500ng/ml had a high sensitivity of 95.7% (low false negative rate) and a low specificity of 8.3% (high false positive rate). However, both the positive and negative likelihood ratios were close to 1, indicating only a slight increase or decrease in probability of pulmonary embolism and therefore non-clinically significant. The committee noted that this evidence came from one study and that the Wells score was not the modified version used in the guideline. The evidence for the usual D-dimer 500ng/mL threshold alone without the use of the Wells score again showed a high sensitivity 96% (low false negative rate) and low specificity 14% (high false positive rate). The positive likelihood ratio was again close to 1 indicating only a slight or non-clinically significant increase in probability of pulmonary embolism with a positive D-dimer test. The negative likelihood ratio 0.28 indicated a moderate and clinically significant decrease in probability of pulmonary embolism with a negative D-dimer test. This was the same with age-adjusted D-dimer tests although it was noted that the sensitivity was slightly lower at 90% relative to the other results and specificity slightly higher at 27.4%. However, the committee acknowledged that there may be an underestimate in the accuracy results as only 2 studies were included in the synthesis of age-adjusted data. Due to a small number of studies, a conservative synthesis approach was performed for the likelihood ratios due to being unable to account for the correlation and trade-off between sensitivity and specificity. The likelihood ratios indicated a slight (non-clinically significant) increase in probability of pulmonary embolism with a positive D-dimer test and a moderate and clinically significant decrease in probability with a negative test. The committee acknowledged the high false positive rate which was expected due to the elevated D-dimers but the low false negative rate due to high sensitivity reassured the committee that the chances of missed diagnosis were still very low in this population. The committee were less concerned about the increased false positive rates because the evidence was from early in the pandemic which is a completely different situation from the context in early 2023 in England (e.g. vaccinated population and less severe disease). The committee discussed that in their experience, there are less severe cases of COVID-19 presenting in this way, so it is unlikely that numbers of false positive rates suggested in the studies will be seen in practice.

There was evidence exploring the possibility of increasing the D-dimer threshold for PE diagnosis in COVID-19. The D-dimer thresholds varied across the evidence ranging from 632ng/mL to 4800ng/mL (without the use of the Wells score) with often only one study reporting on a specific threshold. There was variation in terms of the sensitivity and specificity with each threshold. The committee noted that relative to the usual 500ng/mL D-dimer threshold, as the threshold was increased, there were notable reductions in sensitivity (increased false negative rates) and an increase in specificity (decreased false positive rates). The positive likelihood ratios were higher than 1 indicating a slight to moderate and often clinically significant increase in probability of pulmonary embolism with a positive test and the negative likelihood ratios indicated a slight to moderate and often clinically significant decrease in probability of pulmonary embolism with a negative test. As well as the concerns about the validity of these thresholds, the committee found the increase in false negative rates expected due to reductions in sensitivity to be unacceptable. Whilst some of these studies calculated an optimal D-dimer that maintained a high sensitivity and increased specificity which is reflected in clinically significant likelihood ratios, the uncertainty and low quality of the evidence meant that the committee were unable to use this evidence to suggest increasing D-dimer thresholds or set a threshold for people with COVID-19. As a result, the committee did not think it would be appropriate to make changes to the diagnostic pathway by increasing D-dimer thresholds in people with COVID-19 as this would lead to more missed PE diagnoses. The committee also acknowledged that the Wells score was not included in the diagnostic accuracy data in most studies so was not directly comparable to the pathway in the NG158. Taking into account the uncertainty in the evidence base, the decreasing cases of severe COVID-19 and COVID-19 related VTE and the risk of increasing false negatives by altering D-dimer thresholds, the committee decided not to make a different recommendation for D-dimer testing in people with COVID-19 with suspected PE.

Deep vein thrombosis

The evidence for the standard D-dimer 500ng/mL threshold alone without the use of the Wells suggested a high sensitivity 94.3% (low false negative rate) and low specificity 29.6% (high false positive rate). The positive likelihood ratio was close to 1 indicating only a slight, non-clinically meaningful increase in probability of DVT with a positive D-dimer test. The negative likelihood ratio indicated a large, clinically meaningful decrease in probability of DVT with a negative D-dimer test. The committee noted that this evidence came from one single study with a small sample size (n=106).

There was evidence exploring the possibility of increasing the D-dimer threshold for DVT diagnosis in COVID-19. These D-dimer thresholds ranged from 1500ng/mL to 6494ng/mL (without the use of the Wells score). There was variation in terms of the sensitivity and specificity with each threshold. The committee noted that relative to the usual 500ng/mL D-dimer threshold, as the threshold was increased, there were reductions in sensitivity (increased false negative rates) and an increase in specificity (decreased false positive rates). The likelihood ratios were often above 2 (LR+) or below 0.5 (LR-), indicating clinically significant increases or decreases in the probability of having DVT. However, compared to the PE data, the rates were more variable and the committee acknowledged that this was most likely due to there being smaller sample sizes and generally less data. But that the trend was likely similar to PE. The committee were not confident in using this evidence to alter D-dimer thresholds. Considering this, the committee agreed that it would not be appropriate to make changes to the diagnostic pathway by increasing D-dimer thresholds in people with COVID-19 as this would lead to more missed DVT diagnoses. Taking into account the uncertainty in the evidence base, the decreasing cases of severe COVID-19 and COVID-19 related VTE and the risk of increasing false negatives by altering D-dimer thresholds, the committee decided not to make a different recommendation for D-dimer testing in people with COVID-19 with suspected DVT.

2.1.12.4 Cost effectiveness and resource use

Since no economic studies were found in the literature, the committee discussed the impact on patients and the economic consequences of false positive and false negative test results for PE and DVT.

The consequences of false negative test results can be severe, and can have substantial economic consequences due to longer hospitalisation, intensive care stay, emergency admissions, repeated tests and scans to determine the diagnosis, as well as the downstream effects on health system capacity. However, it can be challenging to quantify the economic impact due to a lack of available data. The economic impact of false positive test results is associated with providing confirmatory scans.

Given that the clinical review included studies deemed to be of moderate to very low quality and were not generalisable to current practice, a resulting economic analysis of all outcomes would not provide generalisable results. Even without a formal comparison, the committee felt that the economic consequences of increased false negatives would outweigh the consequences of false positives. As such, the analysis presented to the committee provides an exploration of the downstream costs of false positives, to aid with decision making.

The committee discussed the size of the population that would be affected by these recommendations to estimate the potential resource impact. Studies on the incidence of PE and DVT in COVID-19 patients were generally undertaken during the first few months of the pandemic and were prior to when vaccination programmes were introduced, and included patients who had been admitted to hospital, with more severe COVID-19 infections. These rates were found to be highly variable between studies (between 7% and 13% for PE, and between 12% and 20% for DVT), and the committee considered that these overestimated the current rate. Therefore, the size of the patient population was estimated using data from a Norwegian study, Tholin et al. (2021), which found an incidence rate of 3.9% of VTE following hospitalisation for COVID-19. The incidence rate in non-hospitalised patients was estimated in the same study and was found to be very low (0.2%). The committee expected that the rate would be negligible in the current COVID-19 climate.

The majority of patients receive computed tomography pulmonary angiograms (CTPA scans) to confirm suspected PE, with ventilation/perfusion (V/Q) scans being used only in the 5% people with contrast allergy or renal impairment. The committee discussed that previously, up to 20% of people would receive V/Q scans, but that practice has changed over the last few years, mostly driven by system pressures caused by the COVID-19 pandemic.

Our analysis estimated that, for a cohort of 1,000 COVID-19 patients suspected of PE, a higher D-dimer thresholds could avoid on average between 138 and 773 false positive results, resulting in savings from averted imaging of between £12,361 and £69,368. For a cohort of 1,000 COVID-19 patients suspected of DVT, between 160 and 460 false positive results would be avoided, resulting in savings of between £10,936 and £31,555. However, the committee noted that all calculations were highly uncertain as they were based on results from studies of low quality and limited generalisability. The number of averted false positives and the subsequent cost savings is likely to be smaller in practice, in the current population with high levels of vaccination and a less severe COVID-19 variant.

The committee felt that there was still a place in practice to use D-dimer assessment in COVID-19 patients, as it was not feasible to recommend that all patients with suspected PE or DVT be sent for confirmatory imaging. This is because of capacity constraints and the burden it would place on the need for imaging in the entire health system.

On balance, the committee felt that the likely savings from averted false positives due to using a higher D-dimer threshold were too uncertain to estimate, and that the risk of increasing false negatives far outweighed these. Moreover, given that the number of hospitalised COVID-19 patients in England for the last 3 months (at 27 February 2023) is 72,670, and considering a low rate of VTE in COVID-19 patients, any potential savings by preventing confirmatory scans would have been relatively small (between £17,966 and £100,819 for PE, and between £15,894 and £45,862 for DVT). The committee felt that would be most appropriate to retain the recommendation with the current D-dimer threshold; and as such, there is no expected resource impact.

1.1.12.5 Other factors the committee took into account

The committee noted that in practice those admitted to hospital for COVID-19 will receive either a prophylactic or therapeutic doses of heparins for VTE prophylaxis due to the increased risk of clotting with COVID-19. This reflects the recommendations in NICE NG191 COVID-19 rapid guideline: managing COVID-19. Considering this, the committee were mindful that in situations where imaging is negative, thromboprophylaxis should be continued in people with COVID-19 requiring oxygen or other respiratory support due to potential underlying immunothrombosis associated with the infection. This process may explain the elevated D-dimers in some cases. The committee acknowledged that it is beyond the scope of standard CTPA to detect capillary immunothrombosis in the lungs. Whilst the committee agreed that a pulmonary ventilation/perfusion (VQ) scan, which is an alternative to CTPA for diagnosing PE, can also detect microvascular disease in the lungs, they acknowledged that these scans are not readily accessible at all hospitals. The committee discussed that further imaging may also increase anxiety in patients and could be technically unfeasible where people with COVID-19 are receiving mechanical ventilation. However, they acknowledged that this scenario is now far less common. The committee agreed that ultimately management or further imaging would be based on clinical judgement.

One of the important factors that the committee took into consideration was the change in COVID-19 context since the research was conducted which has led to dealing with a milder form of the disease and generally higher immunity compared to in the early pandemic. This is reflected in the lower hospitalisation rates for COVID-19 and less severe disease seen in those with the Omicron variant of SARS-CoV-2. However, the committee acknowledged that there is a possibility that this could change should a new variant emerge that causes more severe disease. The committee also discussed that many people may be in hospital for other reasons and COVID-19 is an incidental finding. The committee agreed that there should remain a high level of suspicion of VTE in people with COVID-19 and clinical judgment would be used to take appropriate action, for example where there is clinical worsening or deterioration.

2.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6, 1.1.7, 1.1.11, 1.1.20 and 1.1.21.

2.1.14 References – included studies

2.1.14.1 Diagnostic

Cho, Edward S, McClelland, Paul H, Cheng, Olivia et al. (2021) Utility of d-dimer for diagnosis of deep vein thrombosis in coronavirus disease-19 infection. Journal of vascular surgery. Venous and lymphatic disorders 9(1): 47-53

Gibson, Cameron J, Alqunaibit, Dalia, Smith, Kira E et al. (2020) Probative Value of the D-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome. Critical care medicine 48(12): e1322-e1326

Raj K, Chandna S, Doukas SG et al. (2021) Combined Use of Wells Scores and D-dimer Levels for the Diagnosis of Deep Vein Thrombosis and Pulmonary Embolism in COVID-19: A Retrospective Cohort Study. Cureus 13(9): e17687

Trigonis, Russell A, Holt, Daniel B, Yuan, Rebecca et al. (2020) Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. Critical care medicine 48(9): e805-e808

Appendices

Appendix A: Review protocols

Table 8: Review protocol for diagnosing pulmonary embolism in people with COVID-19

ID	Field	Content
0.	PROSPERO registration number	CRD42023395918
1.	Review title	Clinical probability scores and D-dimer for diagnosing pulmonary embolism in people with COVID-19
2.	Review question	In people with COVID-19 and suspected PE, can we safely rule out the need for further imaging based on a combination of clinical probability score and D-dimer assay?
3.	Objective	• To assess the suitability of using the Wells score and different thresholds of D-dimer testing (conventional, age adjusted, etc) to rule out pulmonary embolism (PE) in people with COVID-19 suspected of having a PE. • To assess economic aspects around using the Wells score and D-dimer testing in this population.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • MEDLINE in Process For economic evidence the following databases will be searched:

		• Medline • Medline in Process • Medline e pubs • Embase • Econlit • International HTA database (INAHTA) Searches will be restricted by: • January 2020 onwards • English language • Human studies • Conference abstracts will be excluded Other searches: Pre-print sources The full search strategies for MEDLINE database will be published in the final review. The MEDLINE strategy will be quality assured (QA) by a trained NICE information specialist. All translated search strategies are peer reviewed to ensure their accuracy. Both procedures are adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. Journal of Clinical Epidemiology, 75, 40-46).
5.	Condition or domain being studied	Pulmonary embolism and COVID-19
6.	Population	Inclusion: Adults (18+ years) with clinically suspected or confirmed COVID-19 within the previous 6 months and who are clinically suspected of having pulmonary embolism (PE)

		COVID-19 confirmed by RT-PCR test or lateral flow test in the absence of RT-PCR test This will also include people with COVID-19 who are hospitalised for another condition and are suspected as having a PE. Exclusion: Pregnant women
7.	Index test	D-dimer test alone or in combination with a pre-test probability using a two-level Wells PE score • Age-adjusted D-dimer test • D-dimer test (without age adjustment – fixed test threshold) 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient Both fixed and age adjusted thresholds will be as defined in the studies. D-dimer tests can either be point of care testing (including qualitative, semi-quantitative and quantitative tests) or laboratory tests 'Point of care' is defined as testing at or near the place and time of patient contact (for example, in an emergency department or GP surgery)
8.	Reference standard	• MRI pulmonary angiography • VQ scan • CT Pulmonary angiography • VTE event at 3 month follow up (for people discharged without imaging as considered low risk)

		NB: Clinical studies often use the recommendations from PIOPED II, PISAPED and CTPA Criteria for Diagnosis of Pulmonary Embolus to determine a positive PE diagnosis.
9.	Types of study to be included	• Diagnostic accuracy cross-sectional studies and cohort studies. • Systematic reviews of diagnostic accuracy cross-sectional studies. • Pre-print publications (non-peer-reviewed) of the above study designs. We will consider the limitations of pre-print studies with the committee which can be accounted for in the committee discussion section in the review. • Where there are no cross-sectional or cohort studies identified, case-control studies will be included. Economic studies: • Economic evaluations • Cost-utility (cost per QALY) • Cost benefit (i.e. Net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimisation • Cost-consequence
10.	Other exclusion criteria	• Non-English language studies. • Diagnostic accuracy studies that do not report sufficient information to allow a 2x2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic accuracy studies where performance of index test depends on the result of the reference test (or vice versa) will be excluded. • Studies using different reference standards across participants based on result of index test

		• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	This is an update of NG158: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing focusing on diagnosing VTE in people with COVID-19. The surveillance review highlighted that those with COVID-19 may present with symptoms that are similar to pulmonary embolism making the diagnoses difficult to distinguish. D-dimer levels can be elevated in people with COVID-19 in the blood due to inflammation. There may also be a higher risk of blood clots associated with COVID-19. Therefore, guidance is needed on the use of the Wells score for pre-test probability and D-dimers in the diagnosis of pulmonary embolism in people with COVID-19.
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy metrics: • Sensitivity/specificity, area under the curve (AUC) Positive and negative likelihood ratios Economic outcomes • Resource use
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers.

		From this point, the remaining abstracts will be screened by a single reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised template in EPPI reviewer 5 will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow. Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual (Appendix H). For diagnostic test accuracy studies, QUADAS-2 will be used.
16.	Strategy for data synthesis	Diagnostic test accuracy (DTA) data will be used to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Meta-analysis of diagnostic accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.1 (Deeks et al. 2022). Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data is not available (2-4 studies), separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using R. This approach is conservative as it is likely to

		somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010). Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Evidence from diagnostic accuracy studies will be initially rated as high-quality, and then downgraded according to the standard GRADE criteria. The choice of primary outcome for decision making will be determined by the committee and GRADE assessments will be undertaken based on these outcomes. This decision will be accounted for and documented as part of the discussion section of the review. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes will be considered. This is done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results.
17.	Analysis of sub-groups	Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) or by whether COVID-19 was confirmed (by PCR or lateral flow test) or clinically suspected where data is available. Where data allows, subgroup analysis may be conducted considering: • Age • COVID-19 disease severity (moderate/severe/critical; may be defined by degree of respiratory support at baseline) • Gender

		• Ethnicity • Time from COVID-19 symptom onset • SARS-CoV-2 variants (or mapping of dates studies were conducted to timing of different COVID-19 waves as a proxy measure) • COVID-19 vaccination status • Treatment setting (outpatient or hospital)		
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	19/01/2023		
22.	Anticipated completion date	16/08/2023		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Funding sources/sponsor	The NICE Guideline Development Team is an internal team within NICE.		
25.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
26.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.		
27.	Other registration details	None		
28.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=395918		
29.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication		

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
30.	Keywords	Diagnosis of pulmonary embolism in people with COVID-19
31.	Details of existing review of same topic by same authors	None
32.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
33..	Additional information	None.
34.	Details of final publication	www.nice.org.uk

Table 8 Review protocol for diagnosing deep vein thrombosis in people with COVID-19

ID	Field	Content
0.	PROSPERO registration number	CRD42023395799
1.	Review title	Clinical probability scores and D-dimer for diagnosing deep vein thrombosis in people with COVID-19

2.	Review question	In people with COVID-19 and suspected DVT, can we safely rule out the need for further imaging based on a combination of clinical probability score and D-dimer assay?
3.	Objective	• To assess the suitability of using the Wells score and different thresholds of D-dimer testing (conventional, age adjusted, etc) to rule out DVT in people with COVID-19 suspected of having a DVT. • To assess economic aspects around using the Wells score and D-dimer testing in this population.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • MEDLINE in Process For economic evidence the following databases will be searched: • Medline • Medline in Process • Medline e pubs • Embase • Econlit • International HTA database (INAHTA) Searches will be restricted by: • January 2020 onwards • English language • Human studies • Conference abstracts will be excluded Other searches:

		• Pre-print sources The full search strategies for MEDLINE database will be published in the final review. The MEDLINE strategy will be quality assured (QA) by a trained NICE information specialist. All translated search strategies are peer reviewed to ensure their accuracy. Both procedures are adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. Journal of Clinical Epidemiology, 75, 40-46).
5.	Condition or domain being studied	Deep vein thrombosis and COVID-19
6.	Population	Inclusion: Adults (18+ years) with clinically suspected or confirmed COVID-19 within the previous 6 months and who are clinically suspected of having deep vein thrombosis (DVT) COVID-19 confirmed by RT-PCR test or lateral flow test in the absence of RT-PCR test This will also include people with COVID-19 who are hospitalised for another condition and are suspected as having a DVT. Exclusion: Pregnant women
7.	Index test	D-dimer test alone or in combination with a pre-test probability score using a two-level Wells DVT score • Age-adjusted D-dimer test

		• D-dimer test (without age adjustment – fixed test threshold) 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient Both fixed and age adjusted thresholds will be as defined in the studies. D-dimer tests can either be point of care testing (including qualitative, semi-quantitative and quantitative tests) or laboratory tests 'Point of care' is defined as testing at or near the place and time of patient contact (for example, in an emergency department or GP surgery)
8.	Reference standard	• Compression ultrasound • Venography • Lower limb MRV scan • Lower limb CT venogram • VTE event at 3 month follow up (for people discharged without imaging as considered low risk)
9.	Types of study to be included	• Diagnostic accuracy cross-sectional studies and cohort studies. • Systematic reviews of diagnostic accuracy cross-sectional studies. • Pre-print publications (non-peer-reviewed) of the above study designs. We will consider the limitations of pre-print studies with the committee which can be accounted for in the committee discussion section in the review.

		• Where there are no cross-sectional or cohort studies identified, case-control studies will be included. Economic studies: • Economic evaluations • Cost-utility (cost per QALY) • Cost benefit (i.e. Net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimisation • Cost-consequence
10.	Other exclusion criteria	• Non-English language studies. • Diagnostic accuracy studies that do not report sufficient information to allow a 2x2 table (TP, FP, TN, FN) to be constructed • Diagnostic accuracy studies where performance of index test depends on the result of the reference test (or vice versa) • Studies using different reference standards across participants based on result of index test Conference abstracts will be excluded
11.	Context	This is an update of NG158: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing focusing on diagnosing VTE in people with COVID-19. D-dimer levels can be elevated in people with COVID-19 in the blood due to inflammation. There may also be a higher risk of blood clots associated with COVID-19. Therefore, guidance is needed on the use of the Wells score for pre-test probability and D-dimers in the diagnosis of DVT in people with COVID-19.
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy metrics: • Sensitivity/specificity, area under the curve (AUC) Positive and negative likelihood ratios Economic outcomes

		• Resource use
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised template in EPPI reviewer 5 will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow. Where appropriate this review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual (Appendix H). For diagnostic test accuracy studies, QUADAS-2 will be used.
16.	Strategy for data synthesis	Diagnostic test accuracy (DTA) data will be used to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and

		true negatives (in people who, according to the reference standard, do not). Meta-analysis of diagnostic accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.1 (Deeks et al. 2022). Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data is not available (2-4 studies), separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using R. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010). Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Evidence from diagnostic accuracy studies will be initially rated as high-quality, and then downgraded according to the standard GRADE criteria. The choice of primary outcome for decision making will be determined by the committee and GRADE assessments will be undertaken based on these outcomes. This decision will be accounted for and documented as part of the discussion section of the review. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes will be considered. This is done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of

		true positive, true negative, false positive and false negative test results.
17.	Analysis of sub-groups	Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) or by whether COVID-19 was confirmed (by PCR or lateral flow test) or clinically suspected where data is available. Where data allows, subgroup analysis may be conducted considering: • Age • COVID-19 disease severity (moderate/severe/critical; may be defined by degree of respiratory support at baseline) • Gender • Ethnicity • Time from COVID-19 symptom onset • SARS-CoV-2 variants (or mapping of dates studies were conducted to timing of different COVID-19 waves as a proxy measure) • COVID-19 vaccination status • Treatment setting (outpatient or hospital)
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	19/01/23

22.	Anticipated completion date	16/8/2023		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Funding sources/sponsor	The NICE Guideline Development Team is an internal team within NICE.		
25.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

26.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
27.	Other registration details	None
28.	Reference/ URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=395799
29.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
30.	Keywords	Diagnosis of deep vein thrombosis in people with COVID-19
31.	Details of existing review of same topic by same authors	None
32.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

33..	Additional information	None
34.	Details of final publication	www.nice.org.uk

Appendix B: Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 20th and 21st December 2022.This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. Systematic Reviews, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. Journal of Clinical Epidemiology, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The searches were based on strategies used in the evidence review for D-dimer testing in the diagnosis of deep vein thrombosis and pulmonary embolism underpinning Venous thromboembolic diseases: diagnosis, management and thrombophilia (2020) NICE guideline NG158. Minor amendments were made. The latest version of the NICE developed COVID population terms was used.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, editorials, news, conferences, comments, historical articles and case reports were applied in adherence to standard NICE practice and the review protocol.

The search was limited to studies published since January 2020 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Key decisions

Eight studies were added to EPPI manually after the searches were completed. These were relevant primary studies identified from systematic reviews retrieved by the searches. They were added by the technical team after cross checking against existing results.

Clinical searches

Table 9 Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	20/12/2022	Wiley	11 of 12 November 2022	45
Cochrane Database of Systematic Reviews (CDSR)	20/12/2022	Wiley	12 of 12 December 2022	0
Embase	20/12/2022	Ovid	1974 to 2022 December 19	1717
MEDLINE	20/12/20222	Ovid	1946 to December 19 2022	463
MEDLINE-in-Process	20/12/2022	Ovid	1946 to December 19 2022	2
MEDLINE Epub Ahead-of-Print	20/12/2022	Ovid	December 19 2022	26
Europe PMC	21/12/2022			1577

Search strategy history

Database name: Medline

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 146043
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 145868
3 (blood* adj1 clot*).ti,ab. 10082
4 or/1-3 230481
5 SARS-CoV-2/ or COVID-19/ 205796
6 (corona* adj1 (virus* or viral*)).ti,ab. 2086
7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 65357
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 214743
9 or/5-8 222859
10 4 and 9 3376
11 Fibrin Fibrinogen Degradation Products/ 10026
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 7434
13 fdp.ti,ab. 3133
14 ("d dimer*" or ddimer*).ti,ab. 13487
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 9824
16 or/11-15 33100
17 10 and 16 633
18 animals/ not humans/ 5041578
19 17 not 18 632
20 limit 19 to ed=20200101-20221220 629
21 limit 20 to english language/ 600
22 (letter or historical article or comment or editorial or news or case reports).pt. 4362880
23 21 not 22 463

Database name: Medline In Process

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 0
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 112
3 (blood* adj1 clot*).ti,ab. 8
4 or/1-3 118
5 SARS-CoV-2/ or COVID-19/ 0
6 (corona* adj1 (virus* or viral*)).ti,ab. 1

7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 179
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 632
9 or/5-8 632
10 4 and 9 11
11 Fibrin Fibrinogen Degradation Products/ 0
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 1
13 fdp.ti,ab. 1
14 ("d dimer*" or ddimer*).ti,ab. 14
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 4
16 or/11-15 18
17 10 and 16 2
18 animals/ not humans/ 0
19 17 not 18 2
20 limit 19 to dt=20200101-20221220 2
21 limit 20 to english language/ 2
22 (letter or historical article or comment or editorial or news or case reports).pt. 737
23 21 not 22 2

Database name: Medline Epub Ahead of Print

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 0
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 1940
3 (blood* adj1 clot*).ti,ab. 173
4 or/1-3 2082
5 SARS-CoV-2/ or COVID-19/ 0
6 (corona* adj1 (virus* or viral*)).ti,ab. 182
7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 3919
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 17223
9 or/5-8 17245
10 4 and 9 169
11 Fibrin Fibrinogen Degradation Products/ 0
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 34
13 fdp.ti,ab. 54
14 ("d dimer*" or ddimer*).ti,ab. 243
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 199
16 or/11-15 506

17 10 and 16 31
18 (letter or historical article or comment or editorial or news or case reports).pt. 19196
19 17 not 18 30
20 limit 19 to english language/ 26

Database name: Embase

1 exp lung embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp vein thrombosis/ or exp deep vein thrombosis/ or exp lower extremity deep vein thrombosis/ or exp upper extremity deep vein thrombosis/ or exp postoperative thrombosis/ or exp leg thrombosis/ 603856
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 238878
3 (blood* adj1 clot*).ti,ab. 15008
4 or/1-3 694464
5 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ 299337
6 (corona* adj1 (virus* or viral*)).ti,ab. 4375
7 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab. 105573
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 356342
9 or/5-8 383028
10 4 and 9 16213
11 fibrin degradation product/ or D dimer/ 40514
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 9277
13 fdp.ti,ab. 4284
14 ("d dimer*" or ddimer*).ti,ab. 27488
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 18055
16 or/11-15 70019
17 10 and 16 4155
18 (letter or editorial or conference).pt. 7397623
19 17 not 18 2712
20 "case report".sh. 2812843
21 19 not 20 1821
22 medline*.db. 9034000
23 21 not 22 1719
24 nonhuman/ not human/ 5112812
25 23 not 24 1717
26 limit 25 to dc=20200101-20221220 1717

Database name: Cochrane (CDSR and CENTRAL)

#1 MeSH descriptor: [Pulmonary Embolism] explode all trees 1128
#2 MeSH descriptor: [Thromboembolism] explode all trees 2322
#3 MeSH descriptor: [Venous Thromboembolism] explode all trees 813

#4 MeSH descriptor: [Venous Thrombosis] explode all trees 2861
#5 MeSH descriptor: [Upper Extremity Deep Vein Thrombosis] explode all trees 24
#6 (((venous or vein) near/1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) near/3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))):ti,ab,kw 20265
#7 (blood* near/1 clot*):ti,ab,kw 6225
#8 {or #1-#7} 27294
#9 MeSH descriptor: [SARS-CoV-2] this term only 1187
#10 MeSH descriptor: [COVID-19] this term only 2553
#11 (corona* near/1 (virus* or viral*)):ti,ab,kw 337
#12 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab 792
#13 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab 14263
#14 {or #9-#13} 14393
#15 #8 and #14 307
#16 MeSH descriptor: [Fibrin Fibrinogen Degradation Products] this term only 544
#17 ((fibrin* or fibrogen) near/4 (product* or fragment* or label*)):ti,ab,kw 1102
#18 (d dimer* or d-dimer*):ti,ab,kw (Word variations have been searched) 2836
#19 (fdp):ti,ab,kw 335
#20 ((wells or Geneva or clinical) near score*):ti,ab,kw 18117
#21 {or #16-#20} 21578
#22 #15 and #21 95
#23 "conference":pt or (clinicaltrials or trialsearch):so 656457
#24 #22 NOT #23 with Cochrane Library publication date Between Jan 2020 and Dec 2022 45

Database name: Europe PMC

(((venous OR vein) AND (thrombosis OR thromboses OR thrombus OR thromboembolism OR stasis* OR clot*)) OR immunothrombo* OR phlebothrombos* OR dvt OR vte OR PE OR “blood clot” OR ((pulmonary OR lung) AND (emboli OR embolus OR emboliz* OR embolis* OR microemboli* OR thromboemboli* OR infarction* OR clot*))) AND (((fibrin* OR fibrogen) AND (product* OR fragment* OR label*)) OR fdp OR "d dimer" OR "d dimers" OR ddimer* OR “wells score” OR “Geneva score” OR “clinical score”) AND((covid* -covidence) OR ((covid or covid19 or covid2019) AND covidence) OR (corona* AND (virus* OR viral*)) OR CoV OR coronavirus* OR 2019nCoV* OR 19nCoV* OR "2019 novel" OR Ncov* OR "n cov" OR (SARS CoV 2*) OR (SARSCoV 2*) OR SARSCoV2* OR (CoV2*) OR (severe acute respiratory syndrome*) OR omicron) AND (FIRST_PDATE:(2020 OR 2021 OR 2022 OR 2023 OR 2024 OR 2025 OR 2026 OR 2027 OR 2028 OR 2029 OR 2030)) AND (SRC:PPR)

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Embase	11/01/2023	Ovid	1974 to 2023 January 10	89
MEDLINE	11/01/2023	Ovid	1946 to January 10 2023	13
MEDLINE-in-Process	11/01/2023	Ovid	1946 to January 10 2023	0
MEDLINE Epub Ahead-of-Print	11/01/2023	Ovid	January 10 2023	3
Econlit	11/01/2023	Ovid	1886 to January 05 2023	0
INAHTA	11/01/2023			0

Search strategy history

Database name: Medline

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 146260
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 146397
3 (blood* adj1 clot*).ti,ab. 10109
4 or/1-3 231094
5 SARS-CoV-2/ or COVID-19/ 208913
6 (corona* adj1 (virus* or viral*)).ti,ab. 2113
7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 66618
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 218072
9 or/5-8 226201
10 4 and 9 3443
11 Fibrin Fibrinogen Degradation Products/ 10031
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 7441
13 fdp.ti,ab. 3139

14 ("d dimer*" or ddimer*).ti,ab. 13565
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 9857
16 or/11-15 33215
17 10 and 16 641
18 animals/ not humans/ 5047592
19 17 not 18 640
20 limit 19 to ed=20200101-20230111 637
21 limit 20 to english language/ 608
22 (letter or historical article or comment or editorial or news or case reports).pt. 4368807
23 21 not 22 469
24 Economics/ 27488
25 exp "Costs and Cost Analysis"/ 262033
26 Economics, Dental/ 1920
27 exp Economics, Hospital/ 25665
28 exp Economics, Medical/ 14377
29 Economics, Nursing/ 4013
30 Economics, Pharmaceutical/ 3092
31 Budgets/ 11665
32 exp Models, Economic/ 16169
33 Markov Chains/ 15879
34 Monte Carlo Method/ 31849
35 Decision Trees/ 12047
36 econom$.tw. 307360
37 cba.tw. 10436
38 cea.tw. 23278
39 cua.tw. 1135
40 markov$.tw. 22399
41 (monte adj carlo).tw. 35464
42 (decision adj3 (tree$ or analys$)).tw. 19982
43 (cost or costs or costing$ or costly or costed).tw. 567737
44 (price$ or pricing$).tw. 41017
45 budget$.tw. 27825
46 expenditure$.tw. 58676
47 (value adj3 (money or monetary)).tw. 2636
48 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 3852
49 or/24-48 1120656
50 "Quality of Life"/ 257247
51 quality of life.tw. 298238
52 "Value of Life"/ 5798
53 Quality-Adjusted Life Years/ 15325
54 quality adjusted life.tw. 14393
55 (qaly$ or qald$ or qale$ or qtime$).tw. 11803
56 disability adjusted life.tw. 4109
57 daly$.tw. 3647
58 Health Status Indicators/ 24074
59 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 26312
60 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 1555

61 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 6331
62 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 33
63 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 412
64 (euroqol or euro qol or eq5d or eq 5d).tw. 13145
65 (qol or hql or hqol or hrqol).tw. 58615
66 (hye or hyes).tw. 63
67 health$ year$ equivalent$.tw. 38
68 utilit$.tw. 214164
69 (hui or hui1 or hui2 or hui3).tw. 1575
70 disutili$.tw. 508
71 rosser.tw. 100
72 quality of wellbeing.tw. 27
73 quality of well-being.tw. 430
74 qwb.tw. 201
75 willingness to pay.tw. 6599
76 standard gamble$.tw. 832
77 time trade off.tw. 1197
78 time tradeoff.tw. 249
79 tto.tw. 1117
80 or/50-79 614180
81 49 or 80 1648826
82 23 and 81 13

Database name: Medline In process

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 0
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 80
3 (blood* adj1 clot*).ti,ab. 6
4 or/1-3 83
5 SARS-CoV-2/ or COVID-19/ 0
6 (corona* adj1 (virus* or viral*)).ti,ab. 1
7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 77
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 307
9 or/5-8 307
10 4 and 9 6
11 Fibrin Fibrinogen Degradation Products/ 0
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 1

13 fdp.ti,ab. 1
14 ("d dimer*" or ddimer*).ti,ab. 6
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 1
16 or/11-15 8
17 10 and 16 0
18 animals/ not humans/ 0
19 17 not 18 0
20 limit 19 to dt=20200101-20230111 0
21 limit 20 to english language/ 0
22 (letter or historical article or comment or editorial or news or case reports).pt. 268
23 21 not 22 0
24 Economics/ 0
25 exp "Costs and Cost Analysis"/ 0
26 Economics, Dental/ 0
27 exp Economics, Hospital/ 0
28 exp Economics, Medical/ 0
29 Economics, Nursing/ 0
30 Economics, Pharmaceutical/ 0
31 Budgets/ 0
32 exp Models, Economic/ 0
33 Markov Chains/ 0
34 Monte Carlo Method/ 0
35 Decision Trees/ 0
36 econom$.tw. 137
37 cba.tw. 1
38 cea.tw. 4
39 cua.tw. 1
40 markov$.tw. 6
41 (monte adj carlo).tw. 11
42 (decision adj3 (tree$ or analys$)).tw. 8
43 (cost or costs or costing$ or costly or costed).tw. 222
44 (price$ or pricing$).tw. 12
45 budget$.tw. 11
46 expenditure$.tw. 19
47 (value adj3 (money or monetary)).tw. 1
48 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 0
49 or/24-48 366
50 "Quality of Life"/ 0
51 quality of life.tw. 145
52 "Value of Life"/ 0
53 Quality-Adjusted Life Years/ 0
54 quality adjusted life.tw. 6
55 (qaly$ or qald$ or qale$ or qtime$).tw. 5
56 disability adjusted life.tw. 1
57 daly$.tw. 1
58 Health Status Indicators/ 0
59 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 5

60 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 0
61 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 1
62 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 0
63 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 0
64 (euroqol or euro qol or eq5d or eq 5d).tw. 15
65 (qol or hql or hqol or hrqol).tw. 39
66 (hye or hyes).tw. 0
67 health$ year$ equivalent$.tw. 0
68 utilit$.tw. 61
69 (hui or hui1 or hui2 or hui3).tw. 3
70 disutili$.tw. 0
71 rosser.tw. 0
72 quality of wellbeing.tw. 0
73 quality of well-being.tw. 0
74 qwb.tw. 0
75 willingness to pay.tw. 1
76 standard gamble$.tw. 0
77 time trade off.tw. 0
78 time tradeoff.tw. 0
79 tto.tw. 0
80 or/50-79 205
81 49 or 80 547
82 23 and 81 0

Database name: Medline Epub Ahead of Print

1 exp pulmonary embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp venous thrombosis/ or exp upper extremity deep vein thrombosis/ 0
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 2023
3 (blood* adj1 clot*).ti,ab. 179
4 or/1-3 2171
5 SARS-CoV-2/ or COVID-19/ 0
6 (corona* adj1 (virus* or viral*)).ti,ab. 190
7 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 4110
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 18097
9 or/5-8 18124
10 4 and 9 169

11 Fibrin Fibrinogen Degradation Products/ 0
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 32
13 fdp.ti,ab. 53
14 ("d dimer*" or "d-dimer*").ti,ab. 244
15 ((wells or Geneva or clinical) adj score*).ti,ab. 195
16 or/11-15 502
17 10 and 16 31
18 (letter or historical article or comment or editorial or news or case reports).pt. 20109
19 17 not 18 31
20 limit 19 to english language/ 28
21 Economics/ 0
22 exp "Costs and Cost Analysis"/ 0
23 Economics, Dental/ 0
24 exp Economics, Hospital/ 0
25 exp Economics, Medical/ 0
26 Economics, Nursing/ 0
27 Economics, Pharmaceutical/ 0
28 Budgets/ 0
29 exp Models, Economic/ 0
30 Markov Chains/ 0
31 Monte Carlo Method/ 0
32 Decision Trees/ 0
33 econom$.tw. 7965
34 cba.tw. 59
35 cea.tw. 249
36 cua.tw. 19
37 markov$.tw. 576
38 (monte adj carlo).tw. 916
39 (decision adj3 (tree$ or analys$)).tw. 701
40 (cost or costs or costing$ or costly or costed).tw. 13188
41 (price$ or pricing$).tw. 1067
42 budget$.tw. 564
43 expenditure$.tw. 1064
44 (value adj3 (money or monetary)).tw. 82
45 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 44
46 or/21-45 22687
47 "Quality of Life"/ 0
48 quality of life.tw. 7532
49 "Value of Life"/ 0
50 Quality-Adjusted Life Years/ 0
51 quality adjusted life.tw. 423
52 (qaly$ or qald$ or qale$ or qtime$).tw. 351
53 disability adjusted life.tw. 121
54 daly$.tw. 107
55 Health Status Indicators/ 0
56 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 394
57 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 46

58 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 142
59 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 0
60 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 6
61 (euroqol or euro qol or eq5d or eq 5d).tw. 504
62 (qol or hql or hqol or hrqol).tw. 1489
63 (hye or hyes).tw. 1
64 health$ year$ equivalent$.tw. 0
65 utilit$.tw. 4405
66 (hui or hui1 or hui2 or hui3).tw. 29
67 disutili$.tw. 17
68 rosser.tw. 0
69 quality of wellbeing.tw. 2
70 quality of well-being.tw. 8
71 qwb.tw. 2
72 willingness to pay.tw. 217
73 standard gamble$.tw. 6
74 time trade off.tw. 29
75 time tradeoff.tw. 0
76 tto.tw. 32
77 or/47-76 12266
78 46 or 77 32971
79 20 and 78 3

Database name: Embase

1 exp lung embolism/ or exp thromboembolism/ or exp venous thromboembolism/ or exp vein thrombosis/ or exp deep vein thrombosis/ or exp lower extremity deep vein thrombosis/ or exp upper extremity deep vein thrombosis/ or exp postoperative thrombosis/ or exp leg thrombosis/ 606383
2 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 239937
3 (blood* adj1 clot*).ti,ab. 15080
4 or/1-3 697429
5 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ 306021
6 (corona* adj1 (virus* or viral*)).ti,ab. 4453
7 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab. 107919
8 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 364209
9 or/5-8 391532
10 4 and 9 16548

11 fibrin degradation product/ or D dimer/ 40900
12 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 9286
13 fdp.ti,ab. 4305
14 ("d dimer*" or ddimer*).ti,ab. 27749
15 ((wells or Geneva or clinical) adj1 score*).ti,ab. 18160
16 or/11-15 70565
17 10 and 16 4232
18 (letter or editorial or conference).pt. 7433019
19 17 not 18 2752
20 "case report".sh. 2822145
21 19 not 20 1845
22 medline*.db. 9058040
23 21 not 22 1742
24 nonhuman/ not human/ 5126929
25 23 not 24 1740
26 limit 25 to dc=20200101-20230111 1740
27 exp Health Economics/ 992689
28 exp "Health Care Cost"/ 329357
29 exp Pharmacoeconomics/ 225004
30 Monte Carlo Method/ 48366
31 Decision Tree/ 19597
32 econom$.tw. 467353
33 cba.tw. 13845
34 cea.tw. 39940
35 cua.tw. 1785
36 markov$.tw. 37751
37 (monte adj carlo).tw. 58325
38 (decision adj3 (tree$ or analys$)).tw. 34459
39 (cost or costs or costing$ or costly or costed).tw. 943525
40 (price$ or pricing$).tw. 69389
41 budget$.tw. 45402
42 expenditure$.tw. 87230
43 (value adj3 (money or monetary)).tw. 4124
44 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 9447
45 or/27-44 2141198
46 "Quality of Life"/ 587865
47 Quality Adjusted Life Year/ 33358
48 Quality of Life Index/ 3104
49 Short Form 36/ 37158
50 Health Status/ 146565
51 quality of life.tw. 556069
52 quality adjusted life.tw. 24986
53 (qaly$ or qald$ or qale$ or qtime$).tw. 25371
54 disability adjusted life.tw. 5809
55 daly$.tw. 5582
56 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 48189
57 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 2829

58 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 11670
59 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 68
60 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 507
61 (euroqol or euro qol or eq5d or eq 5d).tw. 28255
62 (qol or hql or hqol or hrqol).tw. 123680
63 (hye or hyes).tw. 160
64 health$ year$ equivalent$.tw. 41
65 utilit$.tw. 356640
66 (hui or hui1 or hui2 or hui3).tw. 2939
67 disutili$.tw. 1182
68 rosser.tw. 138
69 quality of wellbeing.tw. 69
70 quality of well-being.tw. 552
71 qwb.tw. 266
72 willingness to pay.tw. 12039
73 standard gamble$.tw. 1179
74 time trade off.tw. 1992
75 time tradeoff.tw. 310
76 tto.tw. 2108
77 or/46-76 1225890
78 45 or 77 3171100
79 26 and 78 89

Database name: Econlit

1 (((venous or vein) adj1 (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*)) or immunothrombo* or phlebothrombos* or (dvt or vte or PE) or ((pulmonary or lung) adj3 (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))).ti,ab. 470
2 (blood* adj1 clot*).ti,ab. 2
3 1 or 2 472
4 (corona* adj1 (virus* or viral*)).ti,ab. 39
5 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 197
6 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 9598
7 or/4-6 9625
8 ((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).ti,ab. 0
9 fdp.ti,ab. 42
10 ("d dimer*" or ddimer*).ti,ab. 0
11 ((wells or Geneva or clinical) adj1 score*).ti,ab. 1
12 or/8-11 43

13 3 and 7 and 12 0

Database name: INAHTA

Recent Search History

Combine selections with Export Selected Save Selected Delete Selected

Search History [34 Results] Selected Results [0 Results]

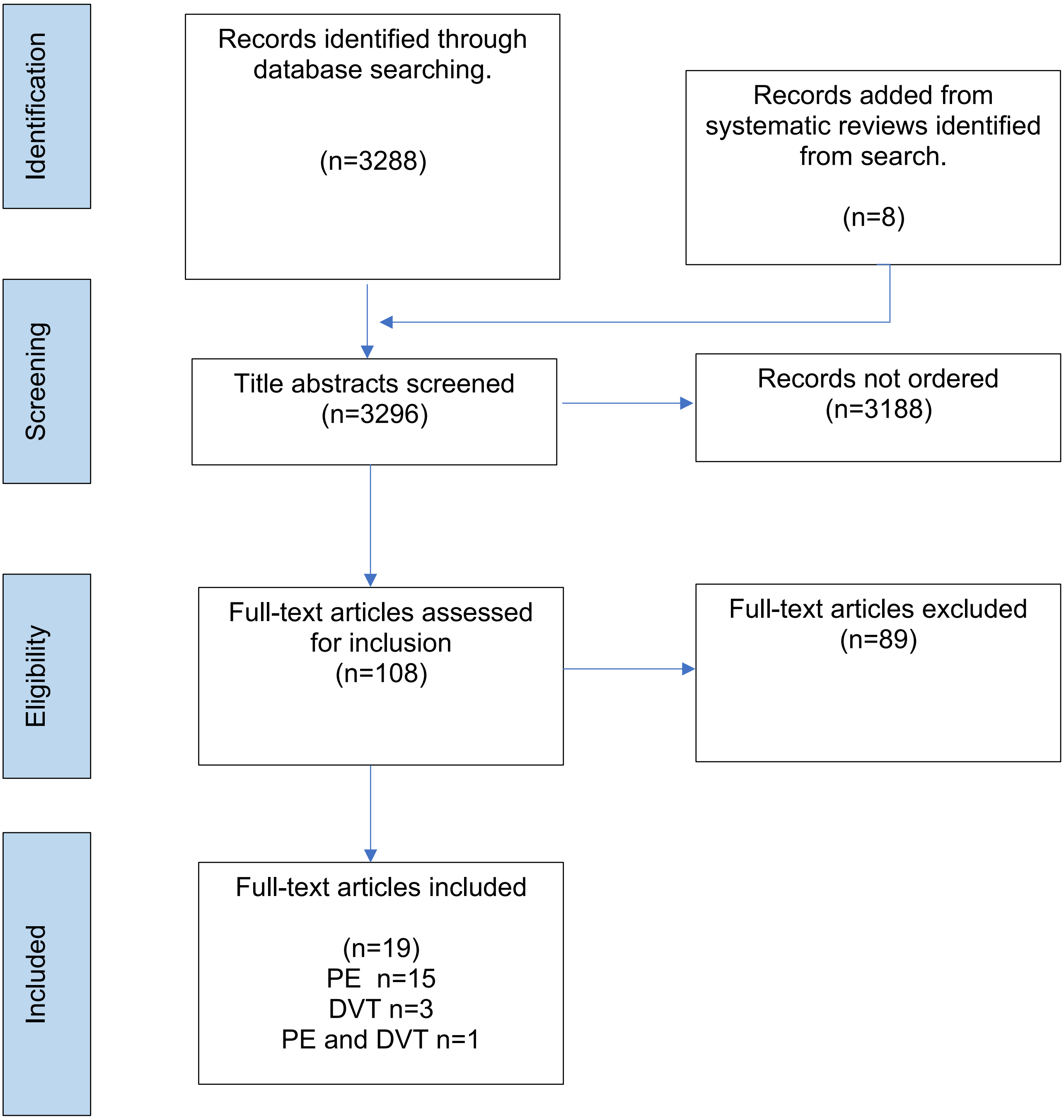
Line	Query	Hits	Date
34	#33 AND #23 AND #16	0	January 11 2023 11:00 AM
33	#32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24	223	January 11 2023 11:00 AM
32	((wells or Geneva or clinical) and score*)[abs]	202	January 11 2023 10:59 AM
31	((wells or Geneva or clinical) and score*)[title]	1	January 11 2023 10:59 AM
30	(d dimer* or d -dimer*)[abs]	9	January 11 2023 10:58 AM
29	(d dimer* or d -dimer*)[title]	4	January 11 2023 10:58 AM
28	(fdp)[abs]	0	January 11 2023 10:56 AM
27	(fdp)[title]	0	January 11 2023 10:56 AM
26	(fibrin* or fibrogen) and (product* or fragment* or label*))[abs]	11	January 11 2023 10:55 AM

25	((fibrin* or fibrogen) and (product* or fragment* or label*))[title]	0	January 11 2023 10:55 AM
24	"Fibrin Fibrinogen Degradation Products"[mh]	1	January 11 2023 10:54 AM
23	#22 OR #21 OR #20 OR #19 OR #18 OR #17	143	January 11 2023 10:53 AM
22	(coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2)[abs]	94	January 11 2023 10:53 AM
21	(coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2)[title]	118	January 11 2023 10:53 AM
20	(corona* and (virus* or viral*))[abs]	3	January 11 2023 10:52 AM
19	(corona* and (virus* or viral*))[title]	0	January 11 2023 10:52 AM
18	"COVID-19"[mh]	126	January 11 2023 10:51 AM
17	"SARS-CoV-2"[mh]	113	January 11 2023 10:51 AM
16	#15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	302	January 11 2023 10:50 AM
15	(blood* and clot*)[abs]	47	January 11 2023 10:49 AM
14	(blood * and clot*)[title]	0	January 11 2023 10:49 AM

13	((pulmonary or lung) and (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))[abs]	77	January 11 2023 10:48 AM
12	((pulmonary or lung) and (emboli or embolus or emboliz* or embolis* or microemboli* or thromboemboli* or infarction* or clot*))[title]	32	January 11 2023 10:48 AM
11	(dvt or vte or PE)[abs]	65	January 11 2023 10:47 AM
10	(dvt or vte or PE)[title]	16	January 11 2023 10:47 AM
9	(immunothrombo* or phlebothrombos*)[abs]	0	January 11 2023 10:46 AM
8	(immunothrombo* or phlebothrombos*)[title]	0	January 11 2023 10:46 AM
7	((venous or vein) and (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*))[abs]	117	January 11 2023 10:45 AM
6	((venous or vein) and (thrombosis or thromboses or thrombus or thromboembolism or stasis* or clot*))[title]	100	January 11 2023 10:45 AM
5	"Upper Extremity Deep Vein Thrombosis"[mhe]	2	January 11 2023 10:43 AM
4	"Venous Thrombosis"[mhe]	89	January 11 2023 10:42 AM
3	"Venous Thromboembolism"[mhe]	68	January 11 2023 10:42 AM
2	"Thromboembolism"[mhe]	103	January 11 2023 10:41 AM
1	"Pulmonary Embolism"[mhe]	42	January 11 2023 10:41 AM

Appendix C: Diagnostic evidence study selection

Figure 1: PRISMA diagram for diagnostic study selection



Appendix D: Diagnostic evidence

Bledsoe, 2022

Bibliographic Reference	Bledsoe, Joseph R; Knox, Daniel; Peltan, Ithan D; Woller, Scott C; Lloyd, James F; Snow, Gregory L; Horne, Benjamin D; Connors, Jean M; Kline, Jeffrey A; D-dimer Thresholds to Exclude Pulmonary Embolism among COVID-19 Patients in the Emergency Department: Derivation with Independent Validation.; Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis; 2022; vol. 28; 10760296221117997

Study Characteristics

Study type	Retrospective cohort study
Study setting	Emergency department
Geographical location	USA
Number of participants	3978 adults with D-dimer result of whom 3583 had COVID-19 infection
Length of follow-up	Not applicable
Inclusion criteria	• positive PCR or antigen test for COVID-19 during or within the 14 days preceding ED visit • serum D-dimer value was measured within 48 h of ED arrival
Exclusion criteria	Patients with DVT and an absence of PE
COVID-19 diagnostic criteria	Positive PCR or antigen test for COVID-19
Time from onset of COVID-19 symptoms	Within 14 days
Definition of clinical suspicion of PE/DVT	Not reported
Use of Wells score	No information reported.
Index test	The primary exposure was the first-available D-dimer within 48 h of ED arrival.

	D-dimer values are reported as fibrinogen equivalent units in both the derivation and validation centres. The Stago STA-LIATEST(R) D-DI assay was used for all tests D-dimer threshold was standard 500 ng/mL cut-off
Reference standard(s)	Chest CT, pulmonary perfusion, or pulmonary ventilation/perfusion scans that were conducted within 48 h of ED arrival
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	Mar-2020
Study end date	Feb-2021
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	This study was a derivation and validation study. In the validation study: • Patient characteristics in the validation cohort were similar to the derivation cohort. • 7748/13091 (59.2%) patients had COVID-19 • 88/7748 (1.14%) had PE (see outcomes for sensitivity and specificity of derived D-dimer cut off) Limitations • Retrospective study • Pre-test probability assessment was not available for these patients. • Unable to assess missed PE diagnosis at 90 days. • Authors assumed that D-dimer orders indicated evaluation for suspected PE, but some laboratory testing may have been obtained for COVID-19 prognostication or evaluation of other suspected processes. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings. • No information on COVID-19 severity
Source of funding	The author(s) received no financial support for the research, authorship, and/or publication of this article.

Study arms

COVID 19 (N = 3583)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 3583)
Male No of events	n = 1728 ; % = 48.2
Female No of events	n = 1855 ; % = 51.8
Age Mean (SD)	61.03 (16.9)
American Indian or Alaska Native No of events	n = 44 ; % = 1.23
Asian No of events	n = 37 ; % = 1.03
Black or African American No of events	n = 45 ; % = 1.26
Multiple race No of events	n = 8 ; % = 0.22
Native Hawaiian or Pacific Islander No of events	n = 128 ; % = 3.57
Declined to say No of events	n = 51 ; % = 1.42
Unavailable No of events	n = 117 ; % = 3.27
Confirmed/suspected COVID-19 No of events	n = 3583 ; % = 100

Characteristic	Study (N = 3583)
History VTE No of events	n = 329 ; % = 9.18
Cancer No of events	n = 412 ; % = 11.5
Obesity No of events	n = 614 ; % = 17.1

Outcomes

Measures of diagnostic accuracy D dimer 0.5 ug/ml

Outcome	COVID 19, , N = 3583
Confirmed pulmonary embolism No of events	n = 148 ; % = 4.1
True positive (TP) Nominal	147
False positive (FP) Nominal	2257
True negative (TN) Nominal	1178
False negative (FN) Nominal	1
Sensitivity As reported in paper Custom value	99.3%
Sensitivity As reported in paper 95% CI	96.8% to 100%
Specificity As reported in paper Custom value	34.3%

Outcome	COVID 19, , N = 3583
Specificity As reported in paper 95% CI	32.7% to 35.9%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.51
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.46 to 1.55
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.03
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.01 to 0.14
Area under the curve Custom value	NR
Area under the curve 95% CI	NR

Measures of diagnostic accuracy D dimer 2 ug/ml

Outcome	COVID 19, , N = 3583
Confirmed pulmonary embolism No of events	n = 148 ; % = 4.1
True positive (TP) Nominal	104
False positive (FP) Nominal	605
True negative (TN) Nominal	2830
False negative (FN)	44

Outcome	**COVID 19, , N = 3583**
Nominal	
Sensitivity As reported in paper Custom value	70.3
Sensitivity As reported in paper 95% CI	62.6 to 77.2
Specificity As reported in paper Custom value	82.4
Specificity As reported in paper 95% CI	81.1 to 83.6
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	3.99
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	3.51 to 4.53
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.36
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.28 to 0.46
Area under the curve Custom value	NR
Area under the curve 95% CI	NR

Validation data for D-dimer cut off <2ug/ml

Outcome	COVID 19, , N = 7748
Sensitivity Nominal	70.5
Sensitivity 95% CI	60.5% to 79.2%
Specificity Nominal	67.8
Specificity 95% CI	66.7% to 68.8%

Validation data for D-dimer cut off 0.5 ug/ml

Outcome	COVID 19, , N = 1343
Sensitivity Nominal	92
Sensitivity 95% CI	85.2% to 96.5%
Specificity Nominal	17
Specificity 95% CI	16.2%% to 17.8%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear if reference standard or index tests were interpreted independently of each other)*
Overall risk of bias and directness	Directness	Directly applicable

Cerda, 2020

Bibliographic Reference	Cerda, Pau; Ribas, Jesus; Iriarte, Adriana; Mora-Lujan, Jose Maria; Torres, Raquel; Del Rio, Belen; Jofre, Hector Ignacio; Ruiz, Yolanda; Huguet, Marta; Fuset, Mari Paz; Martinez-Yelamos, Sergio; Santos, Salud; Llecha, Nuria; Corbella, Xavier; Riera-Mestre, Antoni; Blood test dynamics in hospitalized COVID-19 patients: Potential utility of D-dimer for pulmonary embolism diagnosis.; PloS one; 2020; vol. 15 (no. 12); e0243533

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	Spain
Number of participants	2447 patients with CT scans of which 92 had COVID 19
Length of follow-up	Not applicable
Inclusion criteria	• Patients at least18 years of age • admission for COVID-19 pneumonia • chest CT angiography for clinical suspicion of PE during the study period.
Exclusion criteria	Patients with no contrast-enhanced chest CT scan were excluded, as were patients who were diagnosed with COVID-19 during a hospital stay for other medical conditions
COVID-19 diagnostic criteria	Given the 50%-80% sensitivity for SARS-CoV-2 real-time PCR, patients were also adjudicated as having COVID-19 if CT scan results were considered typical of the disease (i.e., extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation), and if symptoms and/or blood test results were consistent with COVID-19 in the absence of an alternative diagnosis
Time from onset of COVID-19 symptoms	Data from week 2 to week 4 from symptom onset
Definition of clinical suspicion of PE/DVT	Clinical suspicion of PE was defined as new or worsening dyspnoea or oxygen desaturation and/or chest pain, syncope or hemodynamic instability with no other alternative diagnosis.
Use of Wells score	Reported as not being validated in the COVID-19 population.

Index test	D-dimer levels were determined using an ACL TOP 750 System and ACL TOP 500 (Instrumentation Laboratory, Germany). For D-dimer, the upper normal limit was set at 250 μg/L, except for those patients aged over 50 years for whom we used the recommended age adjusted cut-off (age × 10)
Reference standard(s)	Pulmonary CT angiography with 16-slice multi-detector CT (Toshiba Aquilion RXL) after intravenous injection of 60 ml iodinated contrast agent (Rovi Iomeron) at a flow rate of 4 ml/s, triggered on the main pulmonary artery.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Mar-2020
Study end date	24-Apr-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Study does not provide diagnostic accuracy data at the prespecified threshold • The retrospective nature of the study, in which only patients with contrast-enhanced chest CT were considered, makes the real PE incidence difficult to assess. • Small sample size • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. There was no additional external funding received for this study.

Study arms

Patients included (N = 92)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 92)
Male No of events	n = 68 ; % = 73.9
Female No of events	n = 24 ; % = 26.1
Age Mean (SD)	66.9 (26.2)
Caucasian No of events	n = 83 ; % = 90.2
Confirmed/suspected COVID-19 No of events	n = 92 ; % = 100
Oxygen saturation on admission Mean (SD)	93.6 (5.3)
Arterial hypertension No of events	n = 52 ; % = 56.5
VTE thromboprophylaxis for COVID-19 All patients received thromboprophylaxis from admission, except those who were already receiving anticoagulation therapy (3% PE vs 6% non-PE patients) and nine patients diagnosed with PE in the Emergency Department who immediately initiated anticoagulant treatment No of events	n = 92 ; % = 100

Outcomes

Diagnostic accuracy measures D-dimer cut off 632 ug/L

Outcome	Patients included, , N = 92
Confirmed pulmonary embolism No of events	n = 29 ; % = 31.5
True positive (TP) Nominal	26
False positive (FP) Nominal	30
True negative (TN) Nominal	33
False negative (FN) Nominal	3
Sensitivity As reported in paper Custom value	89%
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	53%
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.88
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.41 to 2.51

Outcome	Patients included, , N = 92
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.20
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.07 to 0.59
Area under the curve Custom value	0.727
Area under the curve 95% CI	0.605 to 0.849
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	89.7%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	73.6% to 96.4%
Specificity Calculated by reviewer to obtain 95% CI Custom value	52.4%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	40.3% to 64.2%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Diagnostic accuracy measures not measured for pre-specified threshold)*
Overall risk of bias and directness	Directness	Directly applicable

Cho, 2021

Bibliographic Reference	Cho, Edward S; McClelland, Paul H; Cheng, Olivia; Kim, Yuri; Hu, James; Zenilman, Michael E; D'Ayala, Marcus; Utility of d-dimer for diagnosis of deep vein thrombosis in coronavirus disease-19 infection.; Journal of vascular surgery. Venous and lymphatic disorders; 2021; vol. 9 (no. 1); 47-53

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	USA
Number of participants	158 patients with COVID-19-positive status
Length of follow-up	Not applicable
Inclusion criteria	• COVID 19 positive • had both a D-dimer level and venous duplex ultrasound examinations during their admission
Exclusion criteria	• Aged <18 years • Known DVT or PE before admission
COVID-19 diagnostic criteria	Confirmed COVID-19 status with positive polymerase chain reaction results for severe acute respiratory syndrome coronavirus-2 by nasopharyngeal swab
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical suspicion of PE/DVT	• Those considered high risk for DVT based on clinical criteria (no further information reported)
Use of Wells score	Reported that Wells score has not been validated in COVID-19. Wells score retrospectively calculated. Wells score not included in accuracy analysis.
Index test	D-Dimer measurements were recorded sequentially for all patients throughout their hospital course. Acute-phase D-dimer values, defined as

	the highest D-dimer level before obtaining venous duplex ultrasound examination, were used to compare with the presence of confirmed DVT. Threshold was the conventional reference range of 230ng/ml or less DDU
Reference standard(s)	• Venous duplex ultrasound carried out patient bedside • Venous duplex ultrasound examination was limited to the femoral and popliteal veins and did not include the tibial veins to limit COVID-19 exposure
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Mar-2020
Study end date	13-May-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Retrospective study which made it difficult to obtain important clinical data such as the Wells score. These data were primarily obtained through assessing clinical notes that led up to the decision to perform a venous duplex ultrasound examination and relied on accurate documentation of the patient's clinical condition and medical decision making. • Sample size was relatively small • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	Reported by the authors as "Obtained funding: not applicable"

Study arms

COVID 19 (N = 158)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 158)
Male No of events	n = 85 ; % = 53.8
Female No of events	n = 73 ; % = 46.2
Age Mean (SD)	67.4 (14.6)
Other No of events	n = 22 ; % = 13.9
White or Caucasian No of events	n = 52 ; % = 32.9
Black or African American No of events	n = 77 ; % = 48.7
East Asian or Pacific Islander No of events	n = 7 ; % = 4.4
Non-Hispanic No of events	n = 115 ; % = 81.6
Hispanic No of events	n = 26 ; % = 18.4
Confirmed COVID-19 No of events	n = 158 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0

Characteristic	Study (N = 158)
Mild No of events	n = 0 ; % = 0
Moderate No of events	n = 0 ; % = 0
Severe No of events	n = 158 ; % = 100
Chronic obstructive pulmonary disease No of events	n = 13 ; % = 8.2
Congestive heart failure No of events	n = 11 ; % = 7
Hypertension No of events	n = 113 ; % = 71.5
Acute kidney injury No of events	n = 85 ; % = 53.8
Routine haemodialysis No of events	n = 9 ; % = 5.7
Active malignancy No of events	n = 11 ; % = 7
Disseminated cancer No of events	n = 7 ; % = 4.4
Immobilisation No of events	n = 23 ; % = 14.6
Intubation No of events	n = 92 ; % = 58.6
Sepsis No of events	n = 51 ; % = 32.3
Septic shock No of events	n = 12 ; % = 7.6

Characteristic	Study (N = 158)
VTE thromboprophylaxis for COVID-19 No of events	n = 144 ; % = 91.1
Wells score DVT criteria likely (at least 2) No of events	n = 56 ; % = 35.4

Outcomes

Diagnostic accuracy measure D-dimer 6494 ng/mL

Outcome	COVID 19, , N = 158
Confirmed DVT No of events	n = 52 ; % = 32.9
True positive (TP) Nominal	42
False positive (FP) Nominal	33
True negative (TN) Nominal	73
False negative (FN) Nominal	10
Sensitivity As reported in paper Custom value	80.8%
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	68.9%
Specificity As reported in paper 95% CI	NR

Outcome	COVID 19, , N = 158
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	2.59
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.9 to 3.55
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.28
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.16 to 0.49
Area under the curve Custom value	0.802
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	80.8%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	68.1% to 89.2%
Specificity Calculated by reviewer to obtain 95% CI Custom value	68.9%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	59.5% to 76.9%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear if index test and reference standard were interpreted independently of one another)*
Overall risk of bias and directness	Directness	Directly applicable

Elberts, 2021

Bibliographic Reference	Elberts, Samuel J; Bateman, Ryan; Koutsoubis, Alexandra; London, Kory S; White, Jennifer L; Fields, J Matthew; The impact of COVID-19 on the sensitivity of D-dimer for pulmonary embolism.; Academic emergency medicine : official journal of the Society for Academic Emergency Medicine; 2021; vol. 28 (no. 10); 1142-1149

Study Characteristics

Study type	Cross-sectional study
Study setting	Emergency departments in 3 suburban sites and 2 urban sites
Geographical location	USA
Number of participants	238
Length of follow-up	Not applicable
Inclusion criteria	All emergency department adults who underwent CTPA, D-dimer and COVID-19 testing in a single encounter
Exclusion criteria	Patients were excluded if they did not have a CTPA scan with adequate interpretation, did not undergo D-dimer testing, or did not have a D-dimer test performed within 24 h of the CTPA scan.
COVID-19 diagnostic criteria	Patients were classified as COVID-19 positive if they had a positive COVID test at any point during the encounter. NB: Universal testing for COVID-19 testing was instituted on June 4, 2020, which was mid-way through the study period. Prior to this only patients who were symptomatic or those who were undergoing procedures would have received testing. Type of testing not specified
Time from onset of	Specific time from onset not reported

COVID-19 symptoms	
Definition of clinical suspicion of PE/DVT	Not reported
Use of Wells score	Reported not possible to generate Wells score due to retrospective nature of study.
Index test	Within the health care system, two different immunoturbidimetric D-dimer assays are used. Assay 1 is the STA Liatest D-dimer performed on a Stago platform with a recommended threshold value of 0.50 mg/L fibrinogen equivalent units (FEU). Assay 2 is the HemosIL D-dimer HS, performed on ACL TOP 550 by Instrumentation Laboratory with a recommend threshold value of 230 ng/mL D-dimer units (DDU). The three suburban sites use assay 1 and the two urban sites use assay 2. NB: D-dimer was a part of the admission labs for patients with COVID-19 and empiric anticoagulation was not an institutionally recommended practice
Reference standard(s)	Computed tomography pulmonary angiography All final CTPA reports were reviewed by one of the three study personnel (two resident emergency medicine physicians and one third-year medical student) for presence or absence of acute PE, as reported by the attending radiologist, using a predetermined data abstraction method. Reviewers were blinded to the patient's clinical data except as contained in the radiology report.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Dec-2019
Study end date	22-Oct-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta due to dates

Publication status	Full publication (peer-reviewed)
Additional comments	**Study limitations** • D-dimer taken on admission so not following the existing PE diagnostic pathway i.e. in conjunction with Wells score. • Data very early in pandemic. • No information on COVID-19 severity. • Retrospective study design. • Could introduce selection bias as excluded people who did not have a D-dimer but had CTPA. • Study would have excluded those diagnosed for PE by other methods. • Due to overlap with PE and COVID symptoms, some people who did not have CTPA may have had missed PE diagnosis. • Those without a COVID test prior to universal roll out may have been excluded. • Study authors could not be sure if D-dimers were being used to rule out PE. • In 22% of patients the D-dimer was after the CTPA and therefore definitely could not have been part of prospective decision making. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	Not reported

Study arms

Analysed participants (N = 238)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 238)
Male No of events	n = 121 ; % = 51
Female No of events	n = 117 ; % = 49
Age Mean (SD)	60 (16)

Characteristic	Study (N = 238)
White No of events	n = 110 ; % = 46
Black No of events	n = 92 ; % = 39
Asian No of events	n = 18 ; % = 8
Hispanic No of events	n = 14 ; % = 6
Native American No of events	n = 0 ; % = 0
Unknown No of events	n = 4 ; % = 2
Confirmed/suspected COVID-19 No of events	n = 238 ; % = 100
Hypercoagulable disorder No of events	n = 1 ; % = 0
History of active malignancy No of events	n = 14 ; % = 6
History of VTE No of events	n = 24 ; % = 10

Outcomes

Diagnostic accuracy measures

Outcome	Analysed participants, , N = 238
Confirmed pulmonary embolism No of events	n = 28 ; % = 11.76
True positive (TP) Nominal	28

Outcome	Analysed participants, , N = 238
False positive (FP) Nominal	185
True negative (TN) Nominal	25
False negative (FN) Nominal	0
Sensitivity As reported in paper Custom value	100%
Sensitivity As reported in paper 95% CI	87.66%–100.00%
Specificity As reported in paper Custom value	11.9%
Specificity As reported in paper 95% CI	7.85%–17.07%
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	1.14
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	1.08 to 1.2
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.14
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.01 to 2.28
Area under the curve Assay 1 Custom value	0.76

Outcome	**Analysed participants, , N = 238**
Area under the curve Assay 1 95% CI	0.68-0.83
Area under the curve Assay 2 Custom value	0.85
Area under the curve Assay 2 95% CI	0.77 to 0.92
Sensitivity Calculated by reviewer to adjust for zero cells Custom value	98
Sensitivity Calculated by reviewer to adjust for zero cells 95% CI	85 to 100
Specificity Calculated by reviewer to adjust for zero cells Custom value	8
Specificity Calculated by reviewer to adjust for zero cells 95% CI	8-17
Optimal D-dimer cut-off Assay 1 Custom value	0.67 FEU
Optimal D-dimer cut-off Assay 1 Sensitivity Custom value	100%
Optimal D-dimer cut-off Assay 1 Specificity Custom value	28.9%
Optimal D-dimer cut-off Assay 2 Custom value	662 DDU
Optimal D-dimer cut-off Assay 2 Sensitivity Custom value	100%
Optimal D-dimer cut-off Assay 2 Specificity Custom value	58.5%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable *(Meets PICO but no information on COVID severity or reason for CTPA)*

Estrada, 2022

Bibliographic Reference	Estrada, Víctor Hugo Nieto; Valle, Anacaona Martínez Del; Moreno, Albert Alexander Valencia; Franco, Daniel Leonardo Molano; Álvarez, Elsy Sofía Calle; Perdomo, Daniela Osorio; Ramírez, Carlos Hernán Castañeda; Zárate, Natalia Andrea González; Cáceres, Dayang Sulai Jaramillo; Salazar, Tatiana Andrea Bernal; Rethinking D-dimer’s role in the diagnosis of pulmonary thromboembolism in patients with COVID-19: analysis of a diagnostic test study; 2022

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	University Hospital in Bogota, Columbia
Number of participants	209 Unclear if consecutively recruited
Length of follow-up	Not applicable
Inclusion criteria	• Diagnosed with confirmed COVID-19 • Clinical suspicion of pulmonary embolism
Exclusion criteria	• Absence of D-dimer result • Incomplete clinical data
COVID-19 diagnostic criteria	• COVID-19 confirmed by PCR
Time from onset of COVID-19 symptoms	• Specific time since onset not reported but hospital stay reported as median 5 days IQR 1-99

Definition of clinical suspicion of PE/DVT	Not reported
Use of Wells score	Wells score calculated retrospectively. Wells score ≤4 (unlikely) 159 (76.1%). Wells score not included in accuracy analysis.
Index test	• D-dimer by turbidimetric immunoassay • D-dimer cut off: 499 ng/mL • Unclear if laboratory or point of care test • Wells score was reported but not included as part of the index test
Reference standard(s)	• Computed thoracic angiotomography of pulmonary arteries for diagnosing pulmonary embolism • 64-slice Siemens Emotion Duo tomograph.
Loss to follow-up	Not applicable
Subgroup analysis	None reported
Study end date	Dec-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta based on date
Publication status	Pre-print (not peer reviewed)
Additional comments	• Single-centre retrospective study which will limits the generalisability of the findings. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	This research did not receive any specific grants from funding agencies

Study arms

Analysed participants (N = 209)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 209)
Male No of events	n = 126 ; % = 60.3
Female No of events	n = 83 ; % = 39.7
Age Mean (SD)	60.5 (17.7)
Confirmed COVID-19 cases No of events	n = 209 ; % = 100
Suspected COVID-19 cases No of events	n = 0 ; % = 0
Number with mild COVID-19 severity No of events	n = NR ; % = NR
Number with moderate COVID-19 severity No of events	n = NR ; % = NR
Number with severe COVID-19 severity No of events	n = NR ; % = NR
Number with critical COVID-19 severity Number of people on mechanical ventilation No of events	n = 35 ; % = 16.7
Arterial hypertension No of events	n = 92
Diabetes mellitus No of events	n = 30 ; % = 14.4

Characteristic	Study (N = 209)
COPD No of events	n = 24 ; % = 11.5
Cancer No of events	n = 18 ; % = 8.6
Received anticoagulation (unspecified) No of events	n = 44 ; % = 21.1
Wells Unlikely (≤4) No of events	n = 159 ; % = 76.1

Outcomes

Diagnostic accuracy metrics 499ng/ml D dimer cut off

Outcome	Analysed participants, , N = 209
Confirmed pulmonary embolism by reference standard No of events	n = 30 ; % = 14.4
True positive (TP) Nominal	28
False positive (FP) Nominal	163
True negative (TN) Nominal	16
False negative (FN) Nominal	2
Sensitivity As reported in paper Custom value	93.9%
Sensitivity As reported in paper 95% CI	90.0% to 96.7%

Outcome	Analysed participants, , N = 209
Specificity As reported in paper Custom value	8.9%
Specificity As reported in paper 95% CI	5.1% to 12.8%
Positive likelihood ratio (LR+) as reported in paper Custom value	1.02
Positive likelihood ratio (LR+) as reported in paper 95% CI	0.97 to 1.08
Negative likelihood ratio (LR-) as reported in paper Custom value	0.75
Negative likelihood ratio (LR-) as reported in paper 95% CI	0.36 to 1.54
Area under the curve Custom value	68.4%
Area under the curve 95% CI	NA

Diagnostic accuracy metrics 2281ng/ml D dimer cut off

Outcome	Analysed participants, , N = 209
Confirmed pulmonary embolism No of events	n = 30
True positive (TP) Nominal	18
False positive (FP) Nominal	42

Outcome	Analysed participants, , N = 209
True negative (TN) Nominal	137
False negative (FN) Nominal	12
Sensitivity As reported in paper Custom value	60
Sensitivity As reported in paper 95% CI	53.4 to 66.6
Specificity As reported in paper Custom value	76.9
Specificity As reported in paper 95% CI	70.9 to 82.4
Positive likelihood ratio (LR+) As reported in paper Custom value	2.57
Positive likelihood ratio (LR+) As reported in paper 95% CI	2.1 to 3.14
Negative likelihood ratio (LR-) As reported in paper Custom value	0.52
Negative likelihood ratio (LR-) As reported in paper 95% CI	0.42 to 0.65
Area under the curve Custom value	NR
Area under the curve 95% CI	NR

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Uncertainty around whether interpretation of results was blinded. Risk of selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

Gibson, 2020

Bibliographic Reference	Gibson, Cameron J; Alqunaibit, Dalia; Smith, Kira E; Bronstein, Matthew; Eachempati, Soumitra R; Kelly, Anton G; Lee, Christina; Minneman, Jennifer A; Narayan, Mayur; Shou, Jian; Villegas, Cassandra V; Winchell, Robert J; Barie, Philip S; Probative Value of the D-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome.; Critical care medicine; 2020; vol. 48 (no. 12); e1322-e1326

Study Characteristics

Study type	Retrospective cohort study
Study setting	Hospital
Geographical location	USA
Number of participants	72 intubated patients with critical illness from coronavirus disease 2019
Length of follow-up	Not applicable
Inclusion criteria	Severe COVID
Exclusion criteria	None specified
COVID-19 diagnostic criteria	Confirmed to have SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction analysis of a nasal specimen.
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical	Assessment for LeDVT with two clinical prediction tools, the Wells score and the Dutch Primary Care Rule

suspicion of PE/DVT	
Use of Wells score	Wells score retrospectively calculated. Wells score place all participants at increased risk of DVT. Wells score not included in accuracy analysis.
Index test	D-dimer assays were performed by clot curve analysis on an ACL TOP 700 Laboratory Automation System (Instrumentation Laboratory, Bedford, MA).
Reference standard(s)	lower extremity duplex ultrasonography
Loss to follow-up	Not applicable
Subgroup analysis	None
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported Study dates also not reported but it is mentioned that the cohort had therapeutic anticoagulation in April 2020 so likely to be pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	Screening by the clinical prediction tools lacked probative value; the Wells rule placed every patient at increased risk (usually by virtue of prior immobilization) Limitations • Only screened for lower extremity DVT so some patients may have had DVTs elsewhere or PE without demonstrable DVT • Very limited reporting throughout the study on key information around index tests and reference standard. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	Dr. Barie received funding from Portola, Tetraphase, and several medical malpractice defense attorneys for consultation work. Dr. Narayan received funding from Medcura and Z-Medica. Dr. Winchell received funding from Stryker Corporation (consulting). The remaining authors have disclosed that they do not have any potential conflicts of interest.

Study arms

COVID-19 (N = 72)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 72)
Male No of events	n = 57 ; % = 79
Female No of events	n = 15 ; % = 21
Age Mean only Nominal	64
Confirmed COVID-19 No of events	n = 72 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0
Critical No of events	n = 72 ; % = 100
VTE thromboprophylaxis for COVID-19 No of events	n = 72 ; % = 100

Outcomes

Diagnostic accuracy measures D-dimer 3000ng/mL

Outcome	COVID-19, , N = 72
Confirmed DVT No of events	n = 12 ; % = 16.7
True positive (TP) Nominal	12

Outcome	COVID-19, , N = 72
False positive (FP) Nominal	29
True negative (TN) Nominal	31
False negative (FN) Nominal	0
Sensitivity As reported in paper Custom value	100
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	51.1
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	1.99
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	1.50 to 2.63
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.07
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.01 to 1.14
Area under the curve Custom value	0.874 +/- 0.065

Outcome	COVID-19, , N = 72
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to adjust for zero cells Custom value	96.2
Sensitivity Calculated by reviewer to adjust for zero cells 95% CI	59.7 to 99.8
Specificity Calculated by reviewer to adjust for zero cells Custom value	51.6
Specificity Calculated by reviewer to adjust for zero cells 95% CI	39.3 to 63.8

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Uncertainty around whether index tests and reference standards were interpreted independently of each other. Potential selection bias. Uncertainty around patient flow)*
Overall risk of bias and directness	Directness	Directly applicable

Leonard-Lorant, 2020

Bibliographic Reference	Leonard-Lorant, Ian; Delabranche, Xavier; Severac, Francois; Helms, Julie; Pauzet, Coralie; Collange, Olivier; Schneider, Francis; Labani, Aissam; Bilbault, Pascal; Moliere, Sebastien; Leyendecker, Pierre; Roy, Catherine; Ohana, Mickael; Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels.; Radiology; 2020; vol. 296 (no. 3); e189-e191

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	France
Number of participants	1696 patients with CT scans for COVID-19 suspicion of which 106 had confirmed COVID-19 and pulmonary CT angiography
Length of follow-up	Not applicable
Inclusion criteria	• CT examination including the chest and performed for either suspicion or follow up of COVID • Plus pulmonary angiography
Exclusion criteria	Not reported
COVID-19 diagnostic criteria	All patients who underwent pulmonary CT angiography were evaluated for reverse-transcriptase polymerase chain reaction (RTPCR) results for SARS-CoV-2. All initial samples were obtained by means of nasopharyngeal swab; some patients had a second or third sampling using sputum or bronchoalveolar lavage. Any positive result was classified as confirmed COVID- 19 infection. When RT-PCR results were negative, chest CT images were reviewed by a senior chest radiologist to look for characteristic COVID-19 lung parenchyma lesions. When CT findings were considered typical for COVID-19 (i.e.; extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation) and clinical data were compatible, the patient was also adjudicated as having COVID-19.
Time from onset of COVID-19 symptoms	For PE group: 14 days For non-PE group 10 days
Definition of clinical suspicion of PE/DVT	Not reported NB: Only 63% had CT pulmonary angiography due to PE suspicion
Use of Wells score	Not information reported.
Index test	D-dimer levels were recorded for all patients who underwent pulmonary CT angiography. No D-dimer cut off reported.
Reference standard(s)	Pulmonary CT angiography
Loss to follow-up	Not applicable

Subgroup analysis	None
Study start date	01-Mar-2020
Study end date	31-Mar-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-Delta
Publication status	Full publication (peer-reviewed)
Additional comments	Some concerns around indirectness due to reasons for undergoing CT pulmonary angiography. No pre-specified threshold for D-dimer given. Included 9 negative PCR cases but with typical CT presentation of COVID 19. Authors do not discuss limitations. Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings. Retrospective study design.
Source of funding	Not reported

Study arms

COVID-19 (N = 106)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 106)
Male	n = 70 ; % = 66

Characteristic	Study (N = 106)
No of events	
Female No of events	n = 36 ; % = 34
Age Mean (SD)	63.5 (18.5)
COVID confirmed by RT-PCR No of events	n = 97 ; % = 91.5
COVID diagnosed by CT but with negative PCR No of events	n = 9 ; % = 8.5
VTE thromboprophylaxis for COVID-19 No of events	n = 42 ; % = 39.6

Outcomes

Diagnostic accuracy measures (optimal D-dimer 2660 ug/L)

Outcome	COVID-19 , , N = 106
Confirmed pulmonary embolism No of events	n = 32 ; % = 30
True positive (TP) Nominal	32
False positive (FP) Nominal	24
True negative (TN) Nominal	50
False negative (FN) Nominal	0
Sensitivity Data as reported in paper Custom value	100%

Outcome	COVID-19 , , N = 106
Sensitivity Data as reported in paper 95% CI	88% to 100%
Specificity Data as reported in paper Custom value	67%
Specificity Data as reported in paper 95% CI	52% to 79%
Positive likelihood ratio (LR+) Calculated by reviewer adjusting for zero cells Custom value	3.02
Positive likelihood ratio (LR+) Calculated by reviewer adjusting for zero cells 95% CI	2.173 to 4.184
Negative likelihood ratio (LR-) Calculated by reviewer adjusting for zero cells Custom value	0.023
Negative likelihood ratio (LR-) Calculated by reviewer adjusting for zero cells 95% CI	0.001 to 0.354
Area under the curve Custom value	NR
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer adjusting for zero cells Custom value	99%
Sensitivity Calculated by reviewer adjusting for zero cells 95% CI	80% to 100%

Outcome	COVID-19 , , N = 106
Specificity Calculated by reviewer adjusting for zero cells Custom value	67.6%
Specificity Calculated by reviewer adjusting for zero cells 95% CI	56.3% to 77.1%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Not enough information reported on reference standard and index tests.)*
Overall risk of bias and directness	Directness	Directly applicable

Logothetis, 2021

Bibliographic Reference	Logothetis, Constantine N; Weppelmann, Thomas A; Jordan, Aryanna; Hanna, Catherine; Zhang, Sherry; Charkowick, Shaun; Oxner, Asa; D-Dimer Testing for the Exclusion of Pulmonary Embolism Among Hospitalized Patients With COVID-19.; JAMA network open; 2021; vol. 4 (no. 10); e2128802

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	USA
Number of participants	1541 patients consecutively hospitalised with COVID-19 of which 287 had suspected PE
Length of follow-up	Not applicable
Inclusion criteria	Not specified
Exclusion criteria	Not specified

COVID-19 diagnostic criteria	Not specified
Time from onset of COVID-19 symptoms	Not specified
Definition of clinical suspicion of PE/DVT	Not specified
Use of Wells score	Not information reported.
Index test	• Plasma D-dimer concentrations from an automated, standardized assay (expressed as fibrinogen equivalent units) • The ability of plasma D-dimer concentrations collected the day of CTPA to correctly classify patients with PE was evaluated with a static threshold of 0.5 µg/mL or more (to convert to nanomoles per litre, multiply by 5.476) and an age-adjusted threshold (i.e., D-dimer value, 0.01 × [age − 50 years]) for individuals aged older than 50 years
Reference standard(s)	Computed tomographic pulmonary angiography
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Jan-2020
Study end date	05-Feb-2021
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• The inclusion of patients with D-dimer and CTPA results was necessary to estimate diagnostic performance; however, this may have introduced selection bias by excluding patients unable to undergo CTPA • Published as a research letter so limited details around study characteristics were reported • Study conducted very early in the pandemic.

	• Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings. • Retrospective study design.
Source of funding	Not reported

Study arms

COVID patients with suspected PE (N = 287)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 287)
Male No of events	n = 177 ; % = 61.7
Female No of events	n = 110 ; % = 38.3
Age Mean (SD)	58.2 (16.1)
Required ICU admission during hospitalisation No of events	n = 118 ; % = 41.1

Outcomes

Diagnostic accuracy measures

Outcome	COVID patients with suspected PE, , N = 287
Confirmed pulmonary embolism No of events	n = 37 ; % = 13
True positive (TP) Nominal	37
False positive (FP)	227

Outcome	COVID patients with suspected PE, , N = 287
Nominal	
True negative (TN) Nominal	23
False negative Nominal	0
Sensitivity Data as reported in paper Custom value	100%
Sensitivity Data as reported in paper 95% CI	NR
Specificity Data as reported in paper Custom value	9.3%
Specificity Data as reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	1.09
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	1.03 to 1.15
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.14
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.01 to 2.27
Area under the curve Custom value	0.81%

Outcome	**COVID patients with suspected PE, , N = 287**
Area under the curve 95% CI	NA
Sensitivity Calculated by reviewer to obtain 95% CI and adjust for zero cells Custom value	98.7%
Sensitivity Calculated by reviewer to obtain 95% CI and adjust for zero cells 95% CI	82.2% to 99.9%
Specificity Calculated by reviewer to obtain 95% CI and adjust for zero cells Custom value	9.4%
Specificity Calculated by reviewer to obtain 95% CI and adjust for zero cells 95% CI	6.3% to 13.6%

Critical appraisal - GDT Crit App - QUADAS-2

Section	**Question**	**Answer**
Overall risk of bias and directness	Risk of Bias	Moderate *(Not enough information on whether results of index test and reference standard were interpreted independently)*
Overall risk of bias and directness	Directness	Directly applicable

Mouhat, 2020

Bibliographic Reference	Mouhat, Basile; Besutti, Matthieu; Bouiller, Kevin; Grillet, Franck; Monnin, Charles; Ecarnot, Fiona; Behr, Julien; Capellier, Gilles; Soumagne, Thibaud; Pili-Floury, Sebastien; Besch, Guillaume; Mourey, Guillaume; Lepiller, Quentin; Chirouze, Catherine; Schiele, Francois; Chopard, Romain; Meneveau, Nicolas; Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients.; The European respiratory journal; 2020; vol. 56 (no. 4)

Study Characteristics

Study type	Retrospective cohort study
Study setting	Hospital
Geographical location	France
Number of participants	349 patients admitted with COVID 19 of which 162 had CPTA
Length of follow-up	Followed up until 5th May 2020
Inclusion criteria	• Biologically proven COVID pneumonia (not further described) • Underwent CTPA
Exclusion criteria	Not specified
COVID-19 diagnostic criteria	Laboratory confirmation of SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase (RT)-PCR assay of nasal and pharyngeal swabs
Time from onset of COVID-19 symptoms	Not described but in acute phase
Definition of clinical suspicion of PE/DVT	Clinical signs of severity, namely oxygen saturation measured by pulse oximetry ⩽93% in room air, breathing rate of ⩾30 breaths min^−1 or rapid clinical worsening
Use of Wells score	No information reported.
Index test	D-dimer was done on the day of CTPA No pre-specified threshold used
Reference standard(s)	Multidetector CTPA was performed on a Revolution CT machine (GE Healthcare, Milwaukee, WI, USA) after intravenous injection of 60 mL iodinated contrast agent Imaging results were reviewed by two chest radiologists. Readers were blinded to clinical and biological features. Readers were asked to assess the COVID-19 pattern by quantitative visual CT evaluation.

	In addition, readers were asked to detect presence or absence of PE on CTPA, defined as a filling defect within pulmonary vessels
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	15-Mar-2020
Study end date	16-Apr-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	VTE prevention in COVID-19 patients comprised anticoagulant therapy at different doses, namely, prophylactic dose (low molecular weight heparin (LMWH): subcutaneous enoxaparin 0.4 mg·kg−1 once daily); or therapeutic dose, with either LMWH (s.c. enoxaparin 1 mg·kg−1 twice daily) or unfractionated heparin (UFH): 80 IU·kg−1 bolus dose followed by 18 IU·kg−1 per hour by continuous infusion to achieve an activated partial thromboplastin time ratio between 1.5 and 2.0; or oral anticoagulant. Management of COVID-19 was at the discretion of the physicians in charge. Limitations • Retrospective study from a single centre so presence of unmeasured confounders cannot be excluded. • Relatively small sample size. • Only patients undergoing CTPA were included, and it is thus possible that the actual rate of PE was even higher than reported. • The selection of patients to undergo CTPA was based on clinical criteria of severity that may be debatable. • Most patients did not have compression ultrasonography screening during the study period. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	Not reported

Study arms

COVID 19 (N = 162)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 162)
Male No of events	n = 109 ; % = 67.3
Female No of events	n = 53 ; % = 32.7
Age Mean (SD)	65.57 (13)
Confirmed/suspected COVID-19 No of events	n = 162 ; % = 100
Obesity No of events	n = 42 ; % = 25.9
Hypertension No of events	n = 80 ; % = 49.4
Diabetes mellitus No of events	n = 33 ; % = 20.4
VTE thromboprophylaxis for COVID-19 No of events	n = 141 ; % = 87

Outcomes

Diagnostic accuracy measures (Optimal D-dimer 2590 ng/mL)

Outcome	COVID 19, , N = 162
Confirmed pulmonary embolism No of events	n = 44 ; % = 27.2

Outcome	COVID 19, , N = 162
True positive (TP) Nominal	37
False negative (FP) Nominal	19
True negative (TN) Nominal	99
False negative (FN) Nominal	7
Sensitivity As reported in paper Custom value	83.3%%
Sensitivity As reported in paper 95% CI	68.6% to 93.0%
Specificity (95%CI) As reported in paper Custom value	83.8%
Specificity (95%CI) As reported in paper 95% CI	73.8% to 91.1%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	5.22
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	3.39 to 8.04
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.19
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.10 to 0.38

Outcome	COVID 19, , N = 162
Area under the curve Custom value	0.88
Area under the curve 95% CI	0.809 to 0.932

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Due to uncertainty in patient selection and D-dimer threshold not pre-specified)*
Overall risk of bias and directness	Directness	Directly applicable

Nadeem, 2021

Bibliographic Reference	Nadeem, Iftikhar; Anwar, Asad; Jordon, Louise; Mahdi, Noor; Rasool, Masood Ur; Dakin, Jonathan; Lok, She; Relationship of D-dimer and prediction of pulmonary embolism in hospitalized COVID-19 patients: a multicenter study.; Future microbiology; 2021; vol. 16; 863-870

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospitals
Geographical location	England, UK
Number of participants	193 people with COVID pneumonia
Length of follow-up	NA
Inclusion criteria	Included all patients hospitalized from 1 November 2020 to 31 January 2021 with proven COVID-19 pneumonia and D-Dimer concentration, who underwent computerised tomographic pulmonary angiography (CTPA) due to clinical suspicion of PE. Patients on prior anticoagulant therapy were not excluded from the study cohort.
Exclusion criteria	Not specified

COVID-19 diagnostic criteria	Laboratory confirmation of SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-PCR assay of nasal and pharyngeal swabs.
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical suspicion of PE/DVT	Not defined
Use of Wells score	Wells score calculated retrospectively. Wells score did not differ between PE+ and PE- groups. Reported that Wells score may not be applicable to COVID-19. Wells score not included in accuracy analysis.
Index test	D-dimer was taken on admission Latex agglutination assay was used to measure D-dimer No pre-specified threshold was reported Receiver operating characteristic (ROC) curve analysis was performed and the Youden Index calculated to determine the optimal D-dimer threshold to predict PE
Reference standard(s)	CT pulmonary angiography CTPA findings were recorded (as documented in the report by the site radiologists), including presence of absence of PE and clot burden (quantified by bilateral or unilateral PE findings). Average time interval between admission and CTPA was 36 h.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Nov-2020
Study end date	31-Jan-2021
COVID vaccination	Study conducted before vaccine rollout

COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Dalteparin was given both as prophylaxis and treatment of PE. • The study found that the Wells score correlated poorly with the presence of PE and may not be applicable in patients with COVID-19 pneumonitis. Limitations • A retrospective analysis of patients admitted with COVID-19 who underwent a CTPA so there may have been selection bias, i.e. the patients selected for CTPA were suspected of having high pretest probability of PE. • The sample size was small. • Data was not collected on Doppler ultrasound of legs so DVT cannot be ruled out as the cause of elevated D-Dimers. • No pre-specified D-dimer threshold reported • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	None reported

Study arms

Patients (N = 193)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 193)
Male No of events	n = 102 ; % = 52.8
Female No of events	n = 91 ; % = 47.2
Age Median (PE+ group)	67

Characteristic	Study (N = 193)
Age Median (PE- group)	58
Confirmed COVID-19 No of events	n = 193 ; % = 100
Oxygen saturation (PE+ group) Mean (95% CI)	82.6 (81.5 to 83.7)
Oxygen saturation (PE+ group) Mean (95% CI)	89.1 (87.4 to 90.8)
Anticoagulation treatment on admission No of events	n = 9 ; % = 4.7
Wells score (PE+ group) Mean (95% CI)	1.28 (0.94 to 1.62)
Wells score (PE+ group) Mean (95% CI)	1.86 (1.59 to 2.13)

Outcomes

Diagnostic accuracy measures (D-dimer cut off 2495 ng/ml)

Outcome	Patients, , N = 193
Confirmed pulmonary embolism No of events	n = 33 ; % = 17
True positive (TP) Nominal	33
False positive (FP) Nominal	15
True negative (TN) Nominal	145
False negative (FN) Nominal	0

Outcome	Patients, , N = 193
Sensitivity As reported in paper Custom value	100
Sensitivity As reported in paper 95% CI	100-100
Specificity As reported in paper Custom value	90.62
Specificity As reported in paper 95% CI	90.48 to 90.77
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	10.23
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	6.37 to 16.46
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.02
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.001 to 0.26
Area under the curve Custom value	0.952
Area under the curve 95% CI	0.922 to 0.982
Sensitivity Calculated by reviewer to adjust for zero cells Custom value	98.5

Outcome	Patients, , N = 193
Sensitivity Calculated by reviewer to adjust for zero cells 95% CI	80.4 to 99.9
Specificity Calculated by reviewer to adjust for zero cells Custom value	90.4
Specificity Calculated by reviewer to adjust for zero cells 95% CI	84.8 to 94.1

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Not enough information on whether results of index test and reference standard were interpreted independently. Risk of selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

Polo Friz, 2021

Bibliographic Reference	Polo Friz, Hernan; Gelfi, Elia; Orenti, Annalisa; Motto, Elena; Primitz, Laura; Donzelli, Tino; Intotero, Marcello; Scarpazza, Paolo; Vighi, Giuseppe; Cimminiello, Claudio; Boracchi, Patrizia; Acute pulmonary embolism in patients presenting pulmonary deterioration after hospitalisation for non-critical COVID-19.; Internal medicine journal; 2021; vol. 51 (no. 8); 1236-1242

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	Lombardy, Italy
Number of participants	712 patients with COVID 19 of which 41 had CTPA

Length of follow-up	Not applicable
Inclusion criteria	COVID-19 patients admitted to the internal medicine department (sub intensive and acute general beds of the internal medicine department wards) who had CTPA examinations performed from 1 April to 31 April for respiratory deterioration after admission
Exclusion criteria	History of bleeding diathesis and/or current use of anticoagulant therapy
COVID-19 diagnostic criteria	The diagnosis of COVID-19 was confirmed by RNA detection of the SARS-CoV-2.
Time from onset of COVID-19 symptoms	Time since onset of symptoms to hospitalisation, median (IQR) 8 days (4-12) Time since hospitalisation to CTPA, median (IQR) 11 days (7-17)
Definition of clinical suspicion of PE/DVT	Respiratory deterioration after admission, defined by a reduction of ≥30% of the PaO2/FiO2 ratio
Use of Wells score	Wells score was calculated retrospectively. Patients with <2 points were categorised as PE unlikely and those with ≥2 points were PE likely. Wells score not included as part of accuracy analysis.
Index test	D-dimer was performed 24-48h before performing CTPA D-dimer was measured by using HemosIL D-Dimer HS, a latex-enhanced turbidimetric immunoassay from Instrumentation Laboratory, on the fully automated coagulometer ACL TOP analyser The normal value declared by the producer is <243 ng/mL. Based on a retrospective chart review of clinical symptoms and patient history factors, Wells score simplified version was calculated for each patient, and it was referred to the day when CPTA was performed. One point was given for the presence of each of the following items: (i) previous PE or DVT; (ii) heart rate ≥ 100 b.p. m.; (iii) surgery or immobilisation within the past 4 weeks; (iv) haemoptysis; (v) active cancer; (vi) clinical signs of DVT; and (vii) alternative diagnosis less likely than PE. Patients with <2 points were categorised as PE unlikely and those with ≥2 points were PE likely.

	Since CTPA was performed in subjects suspected by presenting PE in addition to COVID-19 as causing respiratory deterioration, the last item of Wells score (alternative diagnosis less likely than PE) was considered present (1 point) in all cases. The diagnostic performance of different D-dimer cut-offs (standard cut-off: >243 ng/mL, age-adjusted cut-off: patients' age × 5, ROC curve best discriminating value: 2454 ng/mL) and Wells score (standard cut-off: >2) was evaluated
Reference standard(s)	Pulmonary embolism was confirmed on the basis of the presence of a filling defect in one or more pulmonary arteries up to sub-segmental arteries in CTPA, as stated by certified radiologists belonging to the hospital team, at the time of the acquisition of images. Helical CTPA scans were performed on a Brilliance Philips CT scanner (Philips, Cleveland, OH, USA), which included 64-detector row capability.
Subgroup analysis	None
Study start date	01-Apr-2020
Study end date	30-Apr-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	Limitations • Retrospective and monocentric design • Imprecise estimates and generalisability • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings. • No information on COVID-19 severity.
Source of funding	Reported as none

Study arms

COVID 19 (N = 41)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 41)
Male No of events	n = 11 ; % = 26.83
Female No of events	n = 30 ; % = 73.17
Age Median (IQR)	71.7 (63 to 76.2)
Confirmed COVID 19 No of events	n = 41 ; % = 100
Hypertension No of events	n = 29 ; % = 70.73
Diabetes No of events	n = 11 ; % = 26.83
Heparin at prophylactic dose before performing CTPA No of events	n = 4 ; % = 9.76
Heparin at anticoagulant dose before performing CTPA No of events	n = 29 ; % = 70.73
Wells score Median (IQR)	2 (2 to 2)

Outcomes

Diagnostic accuracy measures: standard cut off 243 ng/ml

Outcome	COVID 19, , N = 41
Confirmed pulmonary embolism No of events	n = 8 ; % = 19.51
True positive (TP) Nominal	7
False positive (FP) Nominal	29
True negative (TN) Nominal	4
False negative (FN) Nominal	1
Sensitivity As reported in paper Custom value	88%
Sensitivity As reported in paper 95% CI	47%-99%
Specificity As reported in paper Custom value	12%
Specificity As reported in paper 95% CI	3%-28%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	0.96
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	0.70 to 1.32

Outcome	COVID 19, , N = 41
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	1.26
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.23 to 6.86
Area under the curve Custom value	0.62
Area under the curve 95% CI	0.38 to 0.85

Diagnostic accuracy measures: age-adjusted

Outcome	COVID 19, , N = 41
Confirmed pulmonary embolism No of events	n = 8 ; % = 19.51
True positive (TP) Nominal	7
False positive (FP) Nominal	27
True negative (TN) Nominal	6
False negative (FN) Nominal	1
Sensitivity As reported in paper Custom value	88%
Sensitivity As reported in paper 95% CI	47%-99%
Specificity As reported in paper	18%

Outcome	COVID 19, , N = 41
Custom value	
Specificity As reported in paper 95% CI	7%-35%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.07
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	0.79 to 1.45
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.69
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.10 to 4.94
Area under the curve Custom value	0.62
Area under the curve 95% CI	0.38 to 0.85

Diagnostic accuracy measures: optimal cut off 2454 ng/mL

Outcome	COVID 19, , N = 41
Confirmed pulmonary embolism No of events	n = 8 ; % = 19.51
True positive (TP) Nominal	5
False positive (FP) Nominal	9
True negative (TN) Nominal	24

Outcome	COVID 19, , N = 41
False negative (FN) Nominal	3
Sensitivity As reported in paper Custom value	63%
Sensitivity As reported in paper 95% CI	24% to 91%
Specificity As reported in paper Custom value	73%
Specificity As reported in paper 95% CI	54% to 87%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	2.29
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.06 to 4.97
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.52
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.21 to 1.29
Area under the curve Custom value	0.62
Area under the curve 95% CI	0.38 to 0.85

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Not enough information on whether results of index test and reference standard were interpreted independently)*
Overall risk of bias and directness	Directness	Directly applicable

Quezada-Feijoo, 2021

Bibliographic Reference	Quezada-Feijoo, M.; Ramos, M.; Lozano-Montoya, I.; Sarro, M.; Muinos, V.C.; Ayala, R.; Gomez-Pavon, F.J.; Toro, R.; Elderly population with COVID-19 and the accuracy of clinical scales and d-dimer for pulmonary embolism: The OCTA-COVID study; Journal of Clinical Medicine; 2021; vol. 10 (no. 22); 5433

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	Spain
Number of participants	305 admitted with COVD-19 pneumonia of which 50 were suspected of having pulmonary embolism
Length of follow-up	Not applicable
Inclusion criteria	Patients over 75 years of age hospitalized with COVID-19 with a clinical suspicion of PE
Exclusion criteria	Patients under 75 years of age, those with palliative needs, those diagnosed by the attending team and those who did not meet the diagnostic criteria for COVID-19 were excluded. Patients with a high suspicion of PE who could not undergo a computed tomography (CT) scan and those who declined to participate were also excluded.
COVID-19 diagnostic criteria	SARS-CoV-2 detection was performed using real-time reverse transcriptase-polymerase chain reaction on nasal swabs.
Time from onset of COVID-19 symptoms	Time from clinical symptoms to admission Mean 11 days (SD 22.4) Time from COVID-19 diagnosis to CT scan Mean 8 days (SD 5-10)
Definition of clinical suspicion of PE/DVT	The clinical signs that were assessed included heart rate, breathing rate, oxygen saturation, pain in the deep vein of the lower limb during palpation and unilateral oedema. The risk factors that were considered included atrial fibrillation, deep vein thrombosis (DVT) or PE, cancer, bed rest for more

	than 3 days, newly confirmed DVT events and the presence of associated arterial ischemia.
Use of Wells score	The Wells and revised Geneva scores were calculated to evaluate the probability of PE. Based on the Wells scale, low risk was considered to be less than 2 points, moderate risk from 2 to 6 points and high risk over 6 points.
Index test	D-dimer value used was the peak value either from admission or during the course of hospitalisation. The DD value was adjusted based on the patient's age and was considered elevated when it was above 1 mg/L.
Reference standard(s)	A positive computed tomography pulmonary arteriography (CTPA) confirmed the presence of PE.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	Mar-2020
Study end date	May-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Limited scientific literature on COVID-19 in the elderly population and the associated biomarkers • Confounding biases, including the clinical diagnosis, and limited knowledge of the pathophysiology and biomarkers in COVID-19 patients, need to be supported by future multicentre studies • The incidence of PE could have been underestimated in the early pandemic due to lower numbers referred for CTPA • The dynamic changes in the DD levels from admission to discharge and the low experience with the use of this biomarker in COVID-19 patients could have been influenced by the age of the cohort. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	This work was partially supported by grants from the "New announcement for extraordinary initiative fund UAX-Santander COVID-19", under ID 1.011.103, Universidad Alfonso X el Sabio. This study was also supported by the Fundación Pública Andaluza Progreso y Salud para la Financiación, co-financed by the European Regional Development Fund (ERDF) (PI-0048-

	2017 and PI0033_ 2019), and by a grant from the Spanish Society of Cardiology (SEC) for Basic Research (0011-2019).

Study arms

Suspected PE (N = 50)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 50)
Male No of events	n = 26 ; % = 52
Female No of events	n = 24 ; % = 48
Age (years) Median (IQR)	85.5 (80 to 90)
Confirmed COVID-19 No of events	n = 50 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0
COVID-19 severity CURB-65 Median (IQR)	3 (2 to 3)
Oncological history No of events	n = 10 ; % = 20
DVT No of events	n = 1 ; % = 2
PE No of events	n = 3 ; % = 6
Trauma No of events	n = 1 ; % = 2

Characteristic	Study (N = 50)
Neoplasia in palliative treatment No of events	n = 2 ; % = 4
Lower limbs pain No of events	n = 2 ; % = 4
VTE thromboprophylaxis for COVID-19 No of events	n = 47 ; % = 94
Prophylactic dose No of events	n = 35 ; % = 70
Full anticoagulation No of events	n = 12 ; % = 24

Outcomes

Diagnostic accuracy measures Wells score with optimal D-dimer 4.33 mg/L

Outcome	Suspected PE, , N = 50
Confirmed pulmonary embolism No of events	n = 17 ; % = 34
True positive (TP) Nominal	6
False positive (FP) Nominal	1
True negative (TN) Nominal	32
False negative (FN) Nominal	11
Sensitivity As reported in paper Custom value	35.3%
Sensitivity As reported in paper	NR

Outcome	Suspected PE, , N = 50
95% CI	
Specificity As reported in paper Custom value	96.8
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	11.65
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.52 to 89.09
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.67
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.47 to 0.95
Area under the curve Custom value	NR
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	35.3%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	17.3% to 58.7%
Specificity Calculated by reviewer to obtain 95% CI Custom value	97%

Outcome	Suspected PE, , N = 50
Specificity Calculated by reviewer to obtain 95% CI 95% CI	84.7% to 99.5%

Diagnostic accuracy measures D-dimer cut off >1 mg/L

Outcome	Suspected PE, , N = 50
Confirmed pulmonary embolism No of events	n = 17 ; % = 34
True positive (TP) Nominal	17
False positive (FP) Nominal	23
True negative (TN) Nominal	10
False negative (FN) Nominal	0
Sensitivity As reported in paper Custom value	100
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	30.3
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	1.41

Outcome	Suspected PE, , N = 50
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	1.11 to 1.78
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.09
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.01 to 1.45
Area under the curve Custom value	0.7897
Area under the curve 95% CI	0.652 to 0.927
Sensitivity Calculated by reviewer to adjust for zero cells Custom value	97.2
Sensitivity Calculated by reviewer to adjust for zero cells 95% CI	67.8 to 99.8
Specificity Calculated by reviewer to adjust for zero cells Custom value	30.9
Specificity Calculated by reviewer to adjust for zero cells 95% CI	17.8 to 48

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Some uncertainty around interpretation of results being independent and potential selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

Raj, 2021

Bibliographic Reference	Raj K; Chandna S; Doukas SG; Watts A; Jyotheeswara Pillai K; Anandam A; Singh D; Nagarakanti R; Sankaramangalam K; Combined Use of Wells Scores and D-dimer Levels for the Diagnosis of Deep Vein Thrombosis and Pulmonary Embolism in COVID-19: A Retrospective Cohort Study.; Cureus; 2021; vol. 13 (no. 9)

Study Characteristics

Study type	Retrospective cohort study
Study setting	Hospital
Geographical location	USA
Number of participants	1300 people of which 210 has suspected VTE. 106 had suspected DVT and 109 had suspected PE
Length of follow-up	Not applicable
Inclusion criteria	Patients who had imaging studies for DVT or PE within 90 days of COVID-19 illness were included. The patients with lower extremity (LE) duplex were included in the suspected DVT group, and patients with CT pulmonary angiogram (CT-PA) or V/Q scan were included in the suspected PE group.
Exclusion criteria	None specified
COVID-19 diagnostic criteria	COVID-19 disease is diagnosed with active symptoms of COVID-19 and positive SARS-CoV-2 RT-PCR by nasopharyngeal swab.
Time from onset of COVID-19 symptoms	Patients who had imaging studies for DVT or PE within 90 days of COVID-19 illness were included.
Definition of clinical suspicion of PE/DVT	There was high suspicion for VTE in COVID-19 patients in the study institution so clinicians obtained imaging for VTE based on clinical judgment even when D-dimer or Wells scores were low
Use of Wells score	Wells score was calculated retrospectively. Wells score not included in accuracy analysis with D-dimer.
Index test	D-dimers were obtained within seven days prior to the day of imaging for VTE with most values being drawn 1 to 3 days prior to being tested for VTE

Reference standard(s)	DVT: lower extremity (LE) duplex PE: CT pulmonary angiogram (CT-PA) or V/Q scan
Loss to follow-up	Not applicable
Subgroup analysis	Subgroup analysis by suspected PE or suspected DVT
Study start date	01-Mar-2020
Study end date	01-Dec-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Wells scores are calculated based on information in the charts, which may have led to measurement bias • The authors noted that the prevalence in the study is not true prevalence, as patients were screened based on clinical suspicion • Some patients received empiric anticoagulation over the suspicion of PE but were not included in this study, as they did not have diagnostic testing. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	All authors have declared that no financial support was received from any organisation for the submitted work

Study arms

Suspected DVT (N = 106)

Suspected PE (N = 109)

Population characteristics

Arm-level characteristics

Characteristic	Suspected DVT (N = 106)	Suspected PE (N = 109)
Male No of events	n = 60 ; % = 56.6	n = NR ; % = NR
Female No of events	n = 46 ; % = 43.3	n = NR ; % = NR
Age Mean (SD)	62 (16)	NR (NR)
Confirmed COVID-19 No of events	n = 106 ; % = 100	n = 109 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0	n = 0 ; % = 0
Oxygen saturation Mean (SD)	NR (NR)	95.5 (15.5)
Bedbound No of events	n = 15 ; % = 14.2	n = NR ; % = NR
Active solid cancer No of events	n = 0 ; % = 0	n = NR ; % = NR
Active hematologic cancer No of events	n = 0 ; % = 0	n = NR ; % = NR
History of cancer No of events	n = 5 ; % = 4.9	n = NR ; % = NR

Characteristic	Suspected DVT (N = 106)	Suspected PE (N = 109)
Past history of VTE No of events	n = 5 ; % = 4.9	n = NR ; % = NR
Full dose anticoagulation No of events	n = 7 ; % = 6.6	n = 9 ; % = 8.26
Prophylactic anticoagulation >5 days No of events	n = 35 ; % = 33	n = 30 ; % = 27.5
Wells DVT score <2 No of events	n = 66 ; % = 62.2	n = NA ; % = NA
Wells PE score <2 No of events	n = NA ; % = NA	n = 79 ; % = 72.5
Wells PE score 2-6 No of events	n = NA ; % = NA	n = 22 ; % = 20.2
Wells PE score >6 No of events	n = NA ; % = NA	n = 2 ; % = 1.83

Outcomes

Diagnostic accuracy measures D dimer 1500ng/ml

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
Confirmed pulmonary embolism or DVT No of events	n = 35 ; % = 33	n = 26 ; % = 24.5
True positive (TP) Nominal	26	21
False positive (FP) Nominal	16	12
True negative (TN) Nominal	55	71

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
False negative (FN) Nominal	9	5
Sensitivity As reported in paper Custom value	75	82.6%
Sensitivity As reported in paper 95% CI	NR	NR
Specificity As reported in paper Custom value	77.1%	85.4%
Specificity As reported in paper 95% CI	NR	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	3.30	5.59
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	2.05 to 5.29	3.20 to 9.74
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.33	0.22
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.19 to 0.59	0.1 to 0.5
Area under the curve Custom value	0.8	0.89
Area under the curve 95% CI	NR	NR

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	74.3%	80.8%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	57.9% to 85.8%	62.1% to 91.5%
Specificity Calculated by reviewer to obtain 95% CI Custom value	77.5%	85.5%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	66.5% to 85.6%	76.4% to 91.5%

Diagnostic accuracy measures D dimer 500ng/ml

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
Confirmed pulmonary embolism or DVT No of events	n = 35 ; % = 33	n = 26 ; % = 24.5
True positive (TP) Nominal	33	25
False positive (FP) Nominal	50	39
True negative (TN) Nominal	21	44
False negative (FN) Nominal	2	1
Sensitivity As reported in paper	93.7	95.6

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
Custom value		
Sensitivity As reported in paper 95 % CI	NR	NR
Specificity As reported in paper Custom value	30	53.6
Specificity As reported in paper 95 % CI	NR	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.34	2.01
Positive likelihood ratio (LR+) Calculated by reviewer 95 % CI	1.13 to 1.59	1.57 to 2.57
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.19	0.10
Negative likelihood ratio (LR-) Calculated by reviewer 95 % CI	0.05 to 0.78	0.02 to 0.5
Area under the curve Custom value	0.8	0.89
Area under the curve 95 % CI	NR	NR
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	94.3%	94%
Sensitivity Calculated by reviewer to obtain 95% CI	81.4% to 98.4%	79% to 99%

Outcome	Suspected DVT, , N = 106	Suspected PE, , N = 109
95 % CI		
Specificity Calculated by reviewer to obtain 95% CI Custom value	29.6%	53%
Specificity Calculated by reviewer to obtain 95% CI 95 % CI	20.2% to 41%	42% to 63%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Possibility of selection bias. Not enough information on whether results of index test and reference standard were interpreted independently)*
Overall risk of bias and directness	Directness	Directly applicable

Revel, 2022

Bibliographic Reference	Revel, Marie-Pierre; Beeker, Nathanael; Porcher, Raphael; Jilet, Lea; Fournier, Laure; Rance, Bastien; Chassagnon, Guillaume; Fontenay, Michaela; Sanchez, Olivier; AP-HP /Universities/Inserm COVID-19 research collaboration, AP-HP Covid CDR Initiative; What level of D-dimers can safely exclude pulmonary embolism in COVID-19 patients presenting to the emergency department?.; European radiology; 2022; vol. 32 (no. 4); 2704-2712

Study Characteristics

Study type	Retrospective cohort study
Study setting	Emergency department
Geographical location	France
Number of participants	During the study period, 7,452 adults with SARS-Cov-2 infection confirmed by RT-PCR presented at the ED of AP-HP hospitals and D-dimer dosage was performed for 2,272 of them. Of these, 781 patients had conclusive

	CTPA results obtained within 24 h of D-dimer dosage and composed the study sample
Length of follow-up	Not applicable
Inclusion criteria	Eligible patients were those with a positive reverse transcription-polymerase chain reaction (RT-PCR) result on the nasopharyngeal swab for SARS-Cov-2 who presented to the emergency department (ED) of one of the AP-HP hospitals between March 1 and May 15, 2020, because of respiratory symptoms.
Exclusion criteria	Patients with an indeterminate CTPA result or an unavailable CT report were excluded.
COVID-19 diagnostic criteria	Positive RT-PCR
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical suspicion of PE/DVT	Not described
Use of Wells score	No information reported.
Index test	D-dimer testing was measured using a locally available quantitative and highly sensitive D-dimer assay ELISA VIDAS® D-Dimer Exclusion™ II (bioMérieux SA) Automated latex-enhanced turbidimetric immunoassays: STA®-Liatest® D-Di Plus (Diagnostica Stago) HemosIL D-dimer HS500® (Instrumentation Laboratories) Thresholds used were standard 500ng/mL cut off and age-adjusted
Reference standard(s)	CTPA
Loss to follow-up	Not applicable
Subgroup analysis	By age <50 years and > 50 years

Study start date	01-Mar-2020
Study end date	15-May-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• A selection bias is likely present, since not all COVID-19 patients presenting to the ED with respiratory symptoms had both D-dimer and CTPA systematically performed. 1,442 patients with D-dimer had no CTPA within 24 h of the test. • The authors state that their result should therefore not be interpreted as evaluating the diagnostic performance of D-dimer for PE in COVID-19 patients presenting to the ED with respiratory symptoms. • Central reading of CTPA studies was not performed to confirm or exclude PE. PE diagnosis relied on the conclusion of CTPA reports. • The assay used to measure the level of D-dimer could not be identified for 6 patients of the study sample • There were only 216 patients under the age of 50 in the sample. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	The authors state that this work has not received any funding

Study arms

COVID 19 (N = 781)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 781)
Male No of events	n = 420 ; % = 53.8
Female No of events	n = 361 ; % = 46.2

Characteristic	Study (N = 781)
Age Mean (SD)	62 (17.6)
Confirmed COVID-19 No of events	n = 781 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0
Admitted to normal wards No of events	n = 437 ; % = 56
Admitted to ICU No of events	n = 94 ; % = 12
Hypertension No of events	n = 154 ; % = 19.7
Diabetes No of events	n = 95 ; % = 12.2
Heart failure No of events	n = 42 ; % = 5.4
Chronic kidney disease No of events	n = 25 ; % = 3.2
Body mass index≥30.0 kg/m2 No of events	n = 92 ; % = 11.8

Outcomes

Diagnostic accuracy measures D-dimer 500 ng/mL

Outcome	COVID 19, , N = 781
Confirmed pulmonary embolism No of events	n = 60 ; % = 7.7
True positive (TP) Nominal	59

Outcome	COVID 19, , N = 781
False positive (FP) Nominal	643
True negative (TN) Nominal	78
False negative (FN) Nominal	1
Sensitivity As reported in paper Custom value	98.3%
Sensitivity As reported in paper 95% CI	91.1% to 100%
Specificity As reported in paper Custom value	10.8%
Specificity As reported in paper 95% CI	8.6% to 13.3%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.09
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.04 to 1.15
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.23
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.05 to 1.11
Area under the curve Custom value	0.814

Outcome	COVID 19, , N = 781
Area under the curve 95% CI	0.754 to 0.873

Diagnostic accuracy measures D-dimer age adjusted (Age x 10)

Outcome	COVID 19, , N = 565
Confirmed pulmonary embolism No of events	n = 45 ; % = 7.96
True positive (TP) Nominal	41
False positive (FP) Nominal	346
True negative (TN) Nominal	174
False negative (FN) Nominal	4
Sensitivity As reported in paper Custom value	91.1%
Sensitivity As reported in paper 95% CI	78.8 to 97.5%
Specificity As reported in paper Custom value	33.5%
Specificity As reported in paper 95% CI	29.4 to 37.7%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.37

Outcome	COVID 19, , N = 565
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.23 to 1.53
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.27
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.10 to 0.68
Area under the curve Custom value	0.81
Area under the curve 95% CI	0.740 to 0.881

Diagnostic accuracy measures D-dimer 2000 ng/mL

Outcome	COVID 19, , N = 781
Confirmed pulmonary embolism No of events	n = 60 ; % = 7.7
True positive (TP) Nominal	48
False positive (FP) Nominal	189
True negative (TN) Nominal	532
False negative (FN) Nominal	12
Sensitivity As reported in paper Custom value	80
Sensitivity As reported in paper	67.7 to 89.2

Outcome	**COVID 19, , N = 781**
95% CI	
Specificity As reported in paper Custom value	73.8
Specificity As reported in paper 95% CI	70.4 to 77
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	3.05
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	2.56 to 3.64
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.27
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.16 to 0.45
Area under the curve Custom value	0.814
Area under the curve 95% CI	0.754 to 0.873

Critical appraisal - GDT Crit App - QUADAS-2

Section	**Question**	**Answer**
Overall risk of bias and directness	Risk of Bias	High *(Not enough information on whether results of index test and reference standard were interpreted independently. Risk of selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

Silva, 2021

Bibliographic Reference	Silva, Beatriz Valente; Jorge, Claudia; Placido, Rui; Mendonca, Carlos; Urbano, Maria Luisa; Rodrigues, Tiago; Brito, Joana; da Silva, Pedro Alves; Rigueira, Joana; Pinto, Fausto J; Pulmonary embolism and COVID-19: A comparative analysis of different diagnostic models performance.; The American journal of emergency medicine; 2021; vol. 50; 526-531

Study Characteristics

Study type	Cross-sectional study
Study setting	Emergency department
Geographical location	Lisbon, Portugal
Number of participants	1346 adults who had CTPA of which 300 who were COVID-19 positive and had a D-dimer result
Length of follow-up	Not applicable
Inclusion criteria	Only patients with confirmed SARS-CoV-2 infection in the previous ten days before the ED admission were included.
Exclusion criteria	Patients were excluded if they did not have a D-dimer assay or if CTPA was inconclusive.
COVID-19 diagnostic criteria	The diagnosis of SARS-CoV-2 infection was based on a positive result of real-time reverse transcriptase-polymerase chain reaction assay of nasopharyngeal and pharyngeal swabs or, in patients with prior diagnosis, by consulting the national registration platform of COVID-19 patients.
Time from onset of COVID-19 symptoms	Time between COVID-19 symptoms and CTPA was a median of 4 days (IQR 1-8) in people with PE and a median of 4.5 days (IQR 2-9) in people without PE
Definition of clinical suspicion of PE/DVT	Not described
Use of Wells score	Wells score was retrospectively calculated. Patients were categorised as having low (<4.0 points) ,moderate (4.5–6.0points) or high(≥6.5 points) pretest probability of PE. Wells score was used in diagnostic accuracy analysis.
Index test	Standard approach includes: Wells score

	Patients were categorised as having low(<4.0 points), moderate (4.5–6.0 points) or high (≥6.5points) pretest probability of PE using the Wells score D-dimer Patients classified as high clinical probability on Wells scores are selected to perform CTPA. In contrast, patients with low to moderate clinical probability perform CTPA if they have a D-dimer value above 500ng/mL or above their individual cut-off if an age-adjusted approach was considered. The age-adjusted D-dimer threshold was defined by multiplying the patients' age by 10 in patients above 50 years old.
Reference standard(s)	Computed tomography (CT) was obtained with a16-slice multi- detector CT(Siemens®) after intravenous injection of 60 to 90mL of iodinated contrast agent. The CTPA scans were interpreted by the attending radiologist and reviewed at the time of inclusion in the study by a second radiologist, who was blinded for the clinical information.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Apr-2020
Study end date	31-Jan-2021
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Study is retrospective chart review study so clinical judgment was not made by seeing the patient • Only those with CTPA were included which limits the ability to conclude whether the findings can be applied to the whole emergency department population with PE suspicion • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Study arms

COVID-19 patients (N = 300)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 300)
Male No of events	n = 176 ; % = 58.6
Female No of events	n = 124 ; % = 41.4
Age: PE patients Median (IQR)	76 (65 to 84)
Age: Non-PE patients Median (IQR)	71 (60 to 81)
Confirmed/suspected COVID-19 No of events	n = 300 ; % = 100
Invasive mechanical ventilation No of events	n = 36 ; % = 12
Arterial hypertension No of events	n = 177 ; % = 59
Wells score Median (IQR)	0 (0 to 1.5)
Well score: low risk of PE No of events	n = 289 ; % = 96.3

Outcomes

Diagnostic accuracy measures: Wells <6 plus D-dimer 500ng/ml

Outcome	COVID-19 patients, , N = 300
Confirmed pulmonary embolism No of events	n = 46 ; % = 15.3
True positive (TP) Nominal	44
False positive (FP) Nominal	233
True negative (TN) Nominal	21
False negative (FN) Nominal	2
Sensitivity As reported in paper Custom value	95.65%
Sensitivity As reported in paper 95% CI	85.16% to 99.47%
Specificity As reported in paper Custom value	8.27%
Specificity As reported in paper 95% CI	5.19% to 12.36%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.04
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	0.97 to 1.12

Outcome	COVID-19 patients, , N = 300
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.53
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.13 to 2.17
Area under the curve Custom value	0.52
Area under the curve 95% CI	0.431 to 0.608

Diagnostic accuracy measures: Wells plus D-dimer age-adjusted

Outcome	COVID-19 patients, , N = 300
Confirmed pulmonary embolism No of events	n = 46 ; % = 15.3
True positive (TP) Nominal	41
False positive (FP) Nominal	215
True negative (TN) Nominal	39
False negative (FN) Nominal	5
Sensitivity As reported in the paper Custom value	89.13%
Sensitivity As reported in the paper 95% CI	76.43% to 96.38%
Specificity As reported in the paper	15.35%

Outcome	COVID-19 patients, , N = 300
Custom value	
Specificity As reported in the paper 95% CI	11.15% to 20.39%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.05
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	0.94 to 1.18
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.71
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.29 to 1.7
Area under the curve Custom value	0.521
Area under the curve 95% CI	0.432 to 0.610

Diagnostic accuracy measures: Fixed D-dimer 500ng/ml

Outcome	COVID-19 patients, , N = 300
Confirmed pulmonary embolism No of events	n = 46 ; % = 15.3
True positive (TP) Nominal	44
False positive (FP) Nominal	232
True negative (TN) Nominal	22

Outcome	COVID-19 patients, , N = 300
False negative (FN) Nominal	2
Sensitivity As reported in paper Custom value	95.65%
Sensitivity As reported in paper 95% CI	85.16% to 99.47%
Specificity As reported in paper Custom value	8.66%
Specificity As reported in paper 95% CI	5.51% to 12.82%
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.05
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	0.97 to 1.13
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.5
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.12 to 2.06
Area under the curve Custom value	NR
Area under the curve 95% CI	NR

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Trigonis, 2020

Bibliographic Reference	Trigonis, Russell A; Holt, Daniel B; Yuan, Rebecca; Siddiqui, Asma A; Craft, Mitchell K; Khan, Babar A; Kapoor, Rajat; Rahman, Omar; Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation.; Critical care medicine; 2020; vol. 48 (no. 9); e805-e808

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	USA
Number of participants	45 intubated patients with COVID-19 underwent ultrasound evaluation to identify DVT
Length of follow-up	Not applicable
Inclusion criteria	Patients hospitalised at IU Health Methodist Hospital with confirmed SARS-CoV-2 requiring intubation and mechanical ventilation
Exclusion criteria	None reported
COVID-19 diagnostic criteria	Not reported. Describe only as confirmed SARS-CoV-2
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical suspicion of PE/DVT	Not described
Use of Wells score	No information reported.
Index test	D-dimer values were recorded as the value closest to the date of ultrasound as well as the overall maximum value during the hospitalisation.

	No prespecified threshold
Reference standard(s)	Ultrasound not further described
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	23-Mar-2020
Study end date	08-Apr-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Need for ultrasound was determined at clinician's discretion so may be inconsistent and may have led to selection bias • Author hasn't reported further limitations • Small sample size and limited to those on mechanical ventilation only (severe-critical COVID) • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	National Institutes of Health

Study arms

Intubated patients (N = 45)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 45)
Age (years) Mean (SD)	60.8 (14.9)
White No of events	n = 14 ; % = 31

Characteristic	Study (N = 45)
Black No of events	n = 24 ; % = 53
Other No of events	n = 7 ; % = 16
Confirmed COVID-19 No of events	n = 45 ; % = 100
Clinically suspected COVID-19 No of events	n = 0 ; % = 0
Severe No of events	n = 45 ; % = 100
LMWH 40mg every 24 hr No of events	n = 7 ; % = 16
LMWH 30mg q12h No of events	n = 16 ; % = 35
LMWH 40mg q12h No of events	n = 6 ; % = 13
UFH 5,000 U q8h No of events	n = 10 ; % = 22
UFH 7,500 U q8h No of events	n = 2 ; % = 4
Other No of events	n = 4 ; % = 9

Outcomes

Diagnostic accuracy measures D-dimer 2000ng/mL

Outcome	Intubated patients, , N = 45
Confirmed DVT No of events	n = 19 ; % = 42.2

Outcome	Intubated patients, , N = 45
True positive (TP) Nominal	18
False positive (FP) Nominal	14
True negative (TN) Nominal	12
False negative (FN) Nominal	1
Sensitivity As reported in paper Custom value	95
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	46
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.76
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.21 to 2.55
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.11
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.02 to 0.8

Outcome	Intubated patients, , N = 45
Area under the curve Custom value	NR
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	94.7
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	75.4% to 99.1%
Specificity Calculated by reviewer to obtain 95% CI Custom value	46.2%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	28.8% to 64.5%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Little information around the conduct of the index test and reference standards. Risk of selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

Ventura-Diaz, 2020

Bibliographic Reference	Ventura-Diaz, Sofia; Quintana-Perez, Juan V; Gil-Boronat, Almudena; Herrero-Huertas, Marina; Gorospe-Sarasua, Luis; Montilla, Jose; Acosta-Batlle, Jose; Blazquez-Sanchez, Javier; Vicente-Bartulos, Agustina; A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study.; Emergency radiology; 2020; vol. 27 (no. 6); 679-689

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	Spain
Number of participants	402 people who had CTPA exams of which 242 had COVID 19 and suspected pulmonary embolism
Length of follow-up	Not applicable
Inclusion criteria	People with COVID 19 and suspected pulmonary embolism who had CTPA
Exclusion criteria	People who did not meet COVID 19 diagnostic criteria
COVID-19 diagnostic criteria	The main COVID-19 criterion was a positive result in RTPCR (real-time reverse transcriptase-polymerase chain reaction) testing. However, since the reported sensitivity of RTPCR is somewhat low the combination of typical clinical, laboratory, and imaging (chest x-ray or CT) findings was also considered as COVID-19 criteria, provided that common bacterial and viral pathogens that cause pneumonia were excluded based on microbiological analysis
Time from onset of COVID-19 symptoms	The median time from onset of COVID-19 symptoms to hospital admission was 7 days (IQR 4–13).
Definition of clinical suspicion of PE/DVT	Not described
Use of Wells score	No information reported.
Index test	Threshold for D-dimer was usual laboratory cut off of 500ng/ml No other information provided
Reference standard(s)	• Computed tomography pulmonary angiogram (CTPA) • CTPA exams were performed on a 320-detector CT scanner
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	01-Mar-2020
Study end date	30-Apr-2020

COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Retrospective study conducted at a single centre which may impact the generalisability of the population • Patients were diagnosed in one of the 'red zones' of Europe which could have led to overestimation of negative outcomes in patients due to health system overwhelming. • Confounding factors such as administered treatments, need for mechanical ventilations etc were not examined and could have been helpful in defining the role of Ddimer in estimating PE risk • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings. • No information on COVID-19 severity.
Source of funding	Not reported

Study arms

People with COVID 19 (N = 242)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 242)
Male No of events	n = 151 ; % = 62
Female No of events	n = 91 ; % = 38
Age Median (IQR)	68 (55 to 78)
Confirmed COVID-19 No of events	n = 242 ; % = 100
Clinically suspected COVID-19	n = 0 ; % = 0

Characteristic	Study (N = 242)
No of events	
Comorbidities No of events	n = 176 ; % = 73
Hypertension No of events	n = 102 ; % = 42
Dyslipidaemia No of events	n = 59 ; % = 24
Diabetes No of events	n = 44 ; % = 18
Cancer No of events	n = 24 ; % = 10

Outcomes

Measures of diagnostic accuracy D-dimer 2903 ng/ml

Outcome	People with COVID 19, , N = 242
Confirmed pulmonary embolism No of events	n = 73 ; % = 30
True positive (TP) Nominal	59
False positive (FP) Nominal	69
True negative (TN) Nominal	100
False negative (FN) Nominal	14
Sensitivity As reported in paper Custom value	81%

Outcome	People with COVID 19, , N = 242
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	59%
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.98
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.6 to 2.45
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.32
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.2 to 0.53
Area under the curve Custom value	0.76
Area under the curve 95% CI	0.69 to 0.83
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	80.8%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	70.3% to 88.2%

Outcome	People with COVID 19, , N = 242
Specificity Calculated by reviewer to obtain 95% CI Custom value	59.2%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	51.6% to 66.3%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Unclear if D-dimer and CTPA were interpreted independently of each other. Calculated cut off for D-dimer)*
Overall risk of bias and directness	Directness	Directly applicable

Vivan, 2022

Bibliographic Reference	Vivan, M.A.; Rigatti, B.; da Cunha, S.V.; Frison, G.C.; Antoniazzi, L.Q.; de Oliveira, P.H.K.; Oliveira, J.P.S.; Fontanari, C.; Seligman, B.G.S.; Seligman, R.; Pulmonary embolism in patients with COVID-19 and D-dimer diagnostic value: A retrospective study; Brazilian Journal of Infectious Diseases; 2022; vol. 26 (no. 6); 102702

Study Characteristics

Study type	Cross-sectional study
Study setting	Hospital
Geographical location	Brazil
Number of participants	3683 patients of whom 697 met the inclusion criteria
Length of follow-up	Not applicable
Inclusion criteria	• With SARS-CoV-2 • Had CT angiography

	• Had D-dimers collected within 48 hours before or after CT angiography
Exclusion criteria	Not specified
COVID-19 diagnostic criteria	SARS-CoV-2 was defined as a patient with a positive result in RT-PCR (real-time reverse transcriptase polymerase chain reaction) or antigen testing (immunochromatography); at least two of the signs and symptoms – sudden onset fever, chills, headache, cough, runny nose, sore throat or problems with smell or taste; and who develops dyspnoea, a feeling of heaviness or pressure in the chest, oxygen saturation < 95% or cyanosis.
Time from onset of COVID-19 symptoms	Days of symptoms before admission: Median 8 IQR 5-11
Definition of clinical suspicion of PE/DVT	Not reported
Use of Wells score	Reported as not able to utilise Wells score due to retrospective nature of study.
Index test	• serum D-dimers collected within 48 hours of CTPA • threshold was 0.3 microgram/mL or age adjusted [0.01 x (age -50 years)] • Serum D-dimer levels were evaluated using an automated particle-enhanced quantitative immunoturbidimetric assay (Innovance D-DIMER, Siemens Medical Solutions Diagnostics, Deerfield, IL, USA).
Reference standard(s)	• CT Pulmonary Angiogram • Laboratory results and clinical data related to CTPA were only considered if the interval between CTPA exams and processing of laboratory data was less than 48 hours.
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	Mar-2020
Study end date	May-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta

Publication status	Full publication (peer-reviewed)
Additional comments	• Only included patients with both D-dimer and CTPA results available, which may have introduced selection bias by excluding patients unable to undergo CTPA or that, given the overlap of symptoms with COVID-19, did not have PE suspected. • In the context of COVID-19, D-dimers are routinely ordered to assess prognosis, but the authors could not be sure if the D-dimer was also being used to predict PE, which would select patients with higher D-dimers to undergo CTPA • Retrospective design prevented risk stratification for PE through the application of the Wells score or another tool and made it difficult to control for confounders that could influence the outcomes. • 68% of patients were receiving heparin at prophylactic or therapeutic doses at the time of PE diagnosis and that the authors did not evaluate for other concomitant types of thromboembolism, which may have influenced D-dimer results. • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Study arms

COVID 19 (N = 697)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 697)
Male No of events	n = 382 ; % = 54.8
Female No of events	n = 315 ; % = 45.1
Age Median (IQR)	59 (47 to 67.5)
Confirmed COVID-19 No of events	n = 697 ; % = 100

Characteristic	Study (N = 697)
Clinically suspected COVID-19 No of events	n = 0 ; % = 0
Severe No of events	n = 697 ; % = 100
ICU hospitalization No of events	n = 499 ; % = 71.5
Oxygen supplementation No of events	n = 86 ; % = 12.3
Non-invasive mechanical ventilation No of events	n = 148 ; % = 21.2
Invasive mechanical ventilation No of events	n = 434 ; % = 62.3
Renal replacement therapy (new) No of events	n = 226 ; % = 32.4
Hypertension No of events	n = 389 ; % = 55.8
Diabetes mellitus No of events	n = 212 ; % = 30.4
Chronic kidney disease No of events	n = 76 ; % = 10.9
Renal replacement therapy (previous) No of events	n = 41 ; % = 5.8
Cerebrovascular disease No of events	n = 39 ; % = 5.6
Liver disease No of events	n = 9 ; % = 1.3
Heart disease No of events	n = 87 ; % = 12.5

Characteristic	Study (N = 697)
Neurological disease No of events	n = 24 ; % = 3.4
COPD No of events	n = 46 ; % = 6.6
Asthma No of events	n = 42 ; % = 6
Malignancy No of events	n = 51 ; % = 7.3
Use of immunosuppressant No of events	n = 38 ; % = 5.5
Transplanted No of events	n = 25 ; % = 3.6
HIV No of events	n = 15 ; % = 2.2
VTE thromboprophylaxis for COVID-19 No of events	n = 383 ; % = 54.9

Outcomes

Diagnostic accuracy measures D-dimer cut off 0.3µg/mL

Outcome	COVID 19, , N = 697
Confirmed pulmonary embolism No of events	n = 226 ; % = 32.4
True positive (TP) Nominal	226
False positive (FP) Nominal	465
True negative (TN) Nominal	6

Outcome	COVID 19, , N = 697
False negative (FN) Nominal	0
Sensitivity As reported in paper Custom value	100%
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	1.3%
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells Custom value	1.01
Positive likelihood ratio (LR+) Calculated by reviewer to adjust for zero cells 95% CI	1.00 to 1.02
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells Custom value	0.16
Negative likelihood ratio (LR-) Calculated by reviewer to adjust for zero cells 95% CI	0.01 to 2.83
Area under the curve Custom value	0.77
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to adjust for zero cells	99.8

Outcome	COVID 19, , N = 697
Custom value	
Sensitivity Calculated by reviewer to adjust for zero cells 95% CI	96.6% to 100%
Specificity Calculated by reviewer to adjust for zero cells Custom value	1.4%
Specificity Calculated by reviewer to adjust for zero cells 95% CI	0.6% to 2.9%

Diagnostic accuracy measures D-dimer cut off 0.5μg/mL

Outcome	COVID 19, , N = 697
Confirmed pulmonary embolism No of events	n = 226 ; % = 32.4
True positive (TP) Nominal	222
True negative (TN) Nominal	27
False negative (FN) Nominal	4
Sensitivity As reported in paper Custom value	98.2
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	5.7
Specificity As reported in paper	NR

Outcome	COVID 19, , N = 697
95% CI	
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	1.04
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	1.01 to 1.07
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.31
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.13 to 0.91
Area under the curve Custom value	0.77
Area under the curve 95% CI	NR
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	98%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	95% to 99%
Specificity Calculated by reviewer to obtain 95% CI Custom value	6%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	4% to 8%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(No information reported around whether index test and reference standard were independently interpreted)*
Overall risk of bias and directness	Directness	Directly applicable

Whyte, 2020

Bibliographic Reference	Whyte, Martin B; Kelly, Philip A; Gonzalez, Elisa; Arya, Roopen; Roberts, Lara N; Pulmonary embolism in hospitalised patients with COVID-19.; Thrombosis research; 2020; vol. 195; 95-99

Study Characteristics

Study type	Retrospective cohort study
Study setting	Hospital
Geographical location	UK
Number of participants	1477 patients admitted with COVID-19 of which 214 had CTPA scans for suspected PE
Length of follow-up	Not applicable
Inclusion criteria	• Confirmed or clinically suspected COVID-19 • Had CTPA scan for suspected PE
Exclusion criteria	Not specified
COVID-19 diagnostic criteria	• Detection of COVID-19 was from viral RNA isolated from nasopharyngeal swabs using reverse transcriptase polymerase chain reaction (rtPCR). • Clinically suspected COVID-19 criteria not described
Time from onset of COVID-19 symptoms	Not reported
Definition of clinical suspicion of PE/DVT	PE is most or equally likely was considered present in patients with a sudden unexplained clinical deterioration, e.g. without new changes on chest X-ray. If there was no documentation for a component of the Wells score, it was considered absent. In cases with no documentation in the EPR,

	a Wells score was not calculated. CT scans were requested by the treating clinician for suspected PE.
Use of Wells score	Retrospectively calculated. Not used in accuracy analysis.
Index test	• D-dimer was measured by a latex photometric immunoassay, with STA-Liatest. • Values over 500 ng/mL are considered positive
Reference standard(s)	Computed Tomography Pulmonary Angiogram (CTPA) was performed using a GE Discovery CT750HD (Chicago, Il, USA).
Loss to follow-up	Not applicable
Subgroup analysis	None
Study start date	03-Mar-2020
Study end date	07-May-2020
COVID vaccination	Study conducted before vaccine rollout
COVID variant	Not reported but likely pre-delta
Publication status	Full publication (peer-reviewed)
Additional comments	• Retrospective study so selection bias may have occurred • CTPA request would more likely be made after high D-dimer results, making assessment of the performance of D-dimer challenging. • Retrospective calculation of the Wells score based on author evaluation of the notes up to the time of imaging request relies on accurate recording of comorbidities and clinical features within the notes • Data was collected pre-Delta and pre-COVID vaccination roll out so will affect generalisability of the findings.
Source of funding	Not reported

Study arms

CTPA scans (N = 214)

Population characteristics

Study-level characteristics

Characteristic	Study (N = 214)
Male No of events	n = 129 ; % = 60.2
Female No of events	n = 85 ; % = 39.8
Age Mean (SD)	61.6 (1.45)
Confirmed COVID-19 No of events	n = 145 ; % = 67.8
Clinically suspected COVID-19 No of events	n = 69 ; % = 32.2
Invasive positive pressure ventilation (IPPV), in the intensive care unit (ICU) No of events	n = 78 ; % = 36.4
History of VTE No of events	n = 21 ; % = 9.8
Malignancy No of events	n = 16 ; % = 7.5
VTE thromboprophylaxis for COVID-19 No of events	n = 95 ; % = 44.4
Wells score 'Likely' (4 and over) No of events	n = 53 ; % = 24.8
Wells score 'unlikely' (<4) No of events	n = 158 ; % = 73.8

Outcomes

Diagnostic accuracy measures D-dimer cut-off 4800 ng/mL

Outcome	CTPA scans, , N = 214
Confirmed pulmonary embolism No of events	n = 80 ; % = 37
True positive (TP) Nominal	60
False positive (FP) Nominal	29
True negative (TN) Nominal	105
False negative (FN) Nominal	20
Sensitivity As reported in paper Custom value	75
Sensitivity As reported in paper 95% CI	NR
Specificity As reported in paper Custom value	78
Specificity As reported in paper 95% CI	NR
Positive likelihood ratio (LR+) Calculated by reviewer Custom value	3.47
Positive likelihood ratio (LR+) Calculated by reviewer 95% CI	2.45 to 4.90

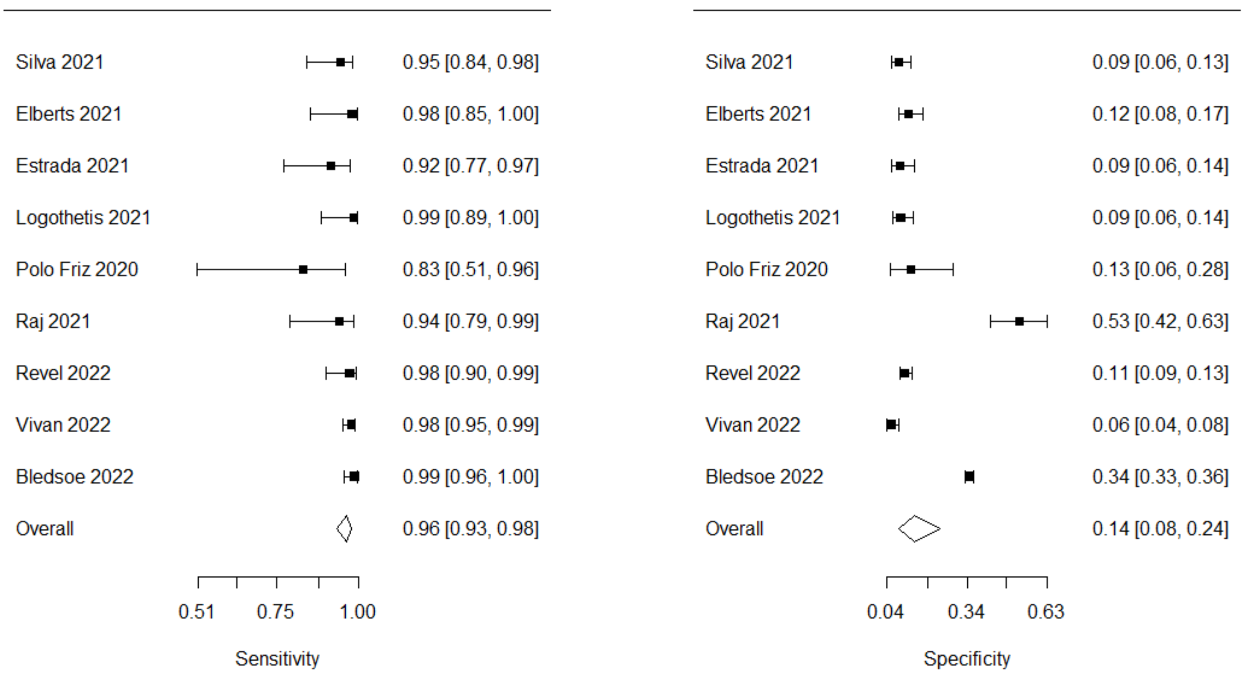
Outcome	CTPA scans, , N = 214
Negative likelihood ratio (LR-) Calculated by reviewer Custom value	0.32
Negative likelihood ratio (LR-) Calculated by reviewer 95% CI	0.22 to 0.47
Area under the curve Custom value	0.772
Area under the curve 95% CI	0.697 to 0.847
Sensitivity Calculated by reviewer to obtain 95% CI Custom value	75%
Sensitivity Calculated by reviewer to obtain 95% CI 95% CI	64.5% to 83.2%
Specificity Calculated by reviewer to obtain 95% CI Custom value	78.4%
Specificity Calculated by reviewer to obtain 95% CI 95% CI	70.6% to 84.5%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(D-dimer results may have led to referral for CTPA. Potential selection bias)*
Overall risk of bias and directness	Directness	Directly applicable

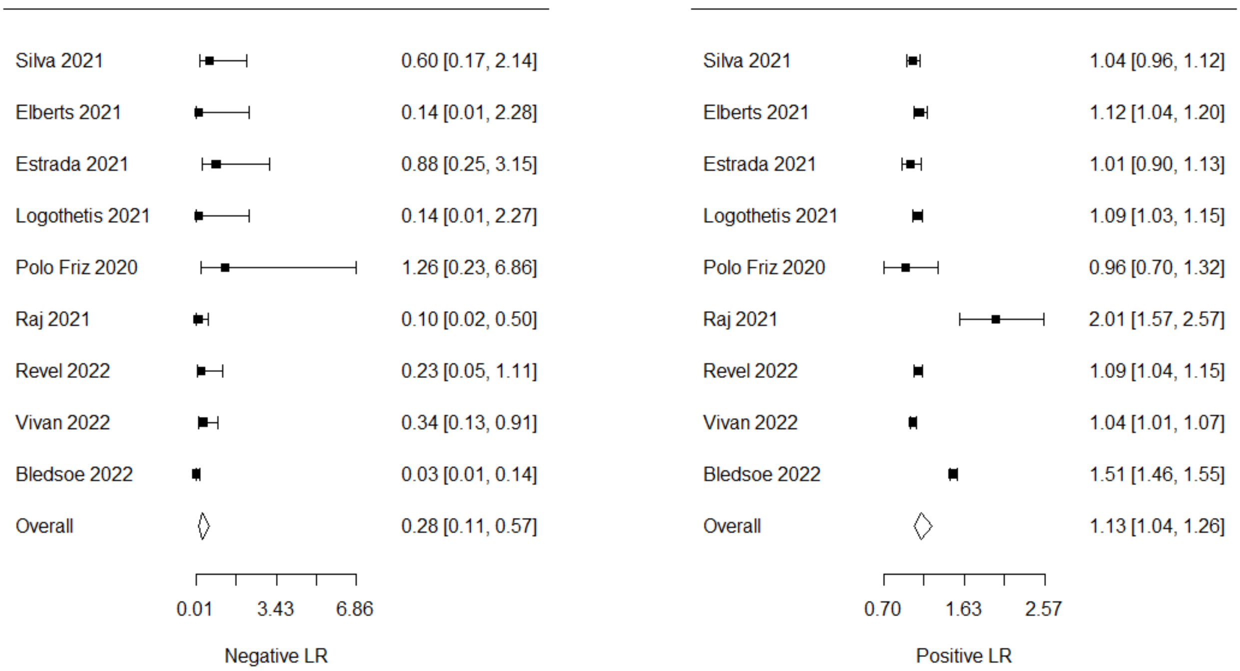
Appendix E: Forest plots

Figure 2: Sensitivity and Specificity for D-dimer with a threshold of 500ng/ml (no Wells score) for pulmonary embolism (random effects)



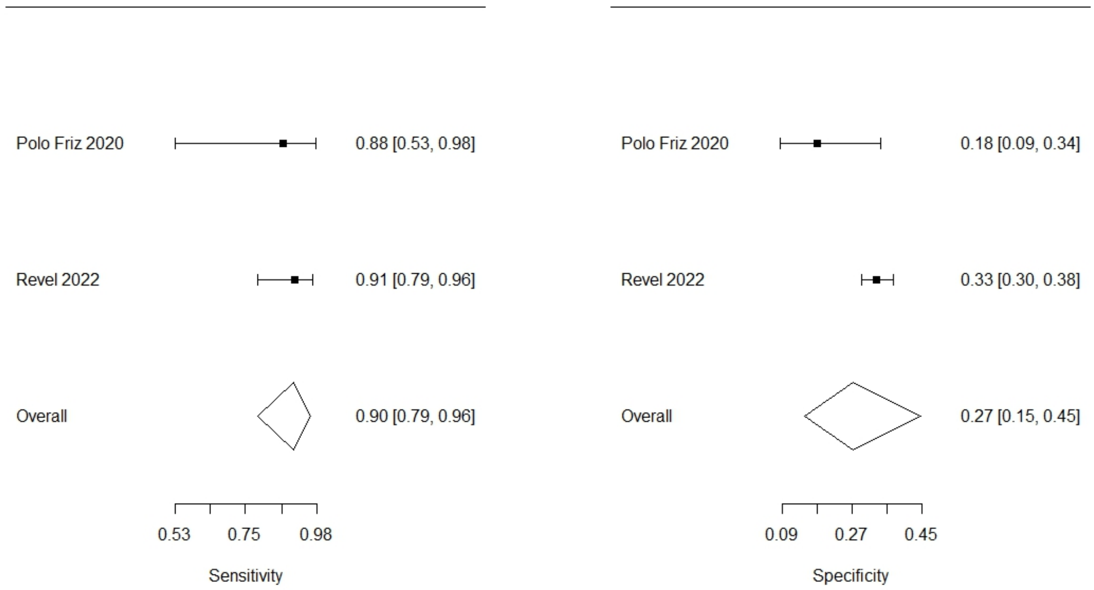
I^2 (sensitivity) = 0%, I^2 specificity = 98%

Figure 3: Likelihood ratios for D-dimer with a threshold of 500ng/ml (no Wells score) for pulmonary embolism (random effects)



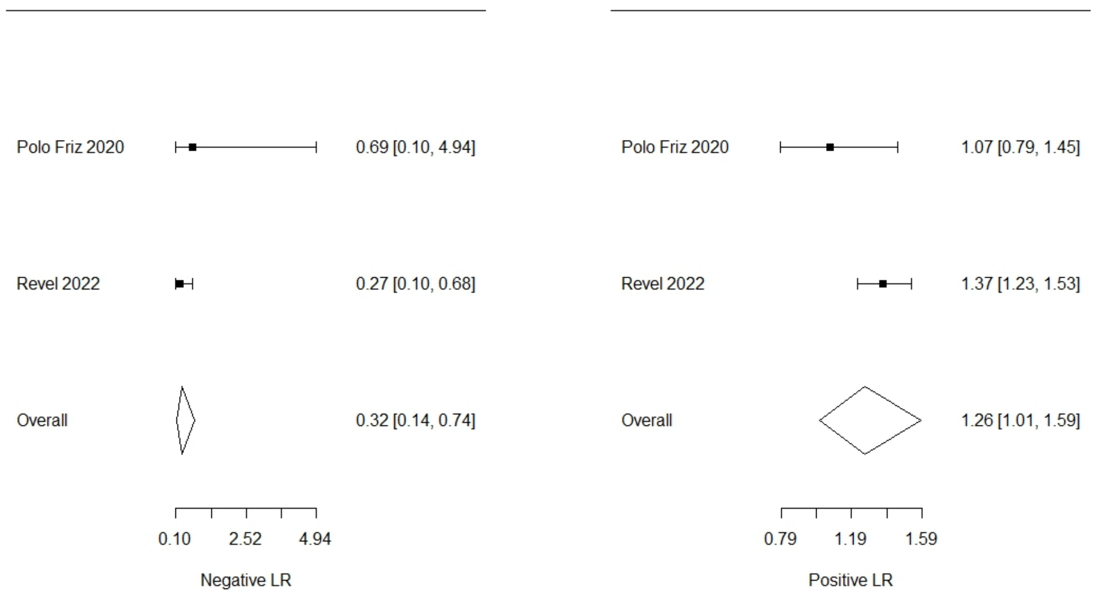
I^2 (negative LR) = 42.1%, I^2 positive LR = 98.2%

Figure 4: Sensitivity and Specificity for Age-adjusted D-dimer (no Wells score) for pulmonary embolism (random effects)



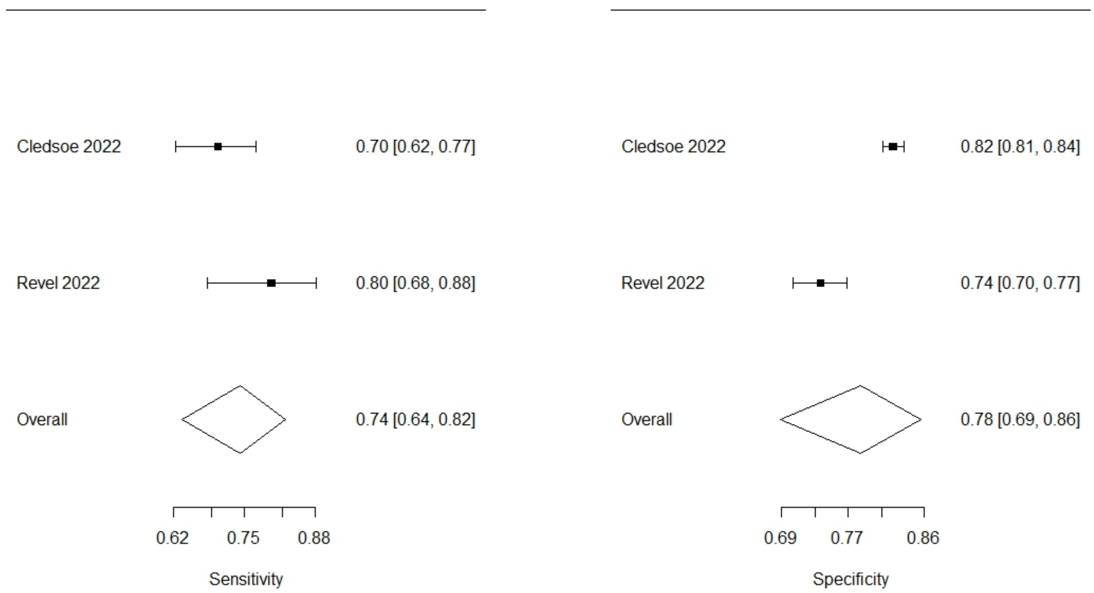
I^2 (sensitivity) = 0%, I^2 specificity = 68.2%

Figure 5: Likelihood ratios for Age-adjusted D-dimer (no Wells score) for pulmonary embolism (random effects)



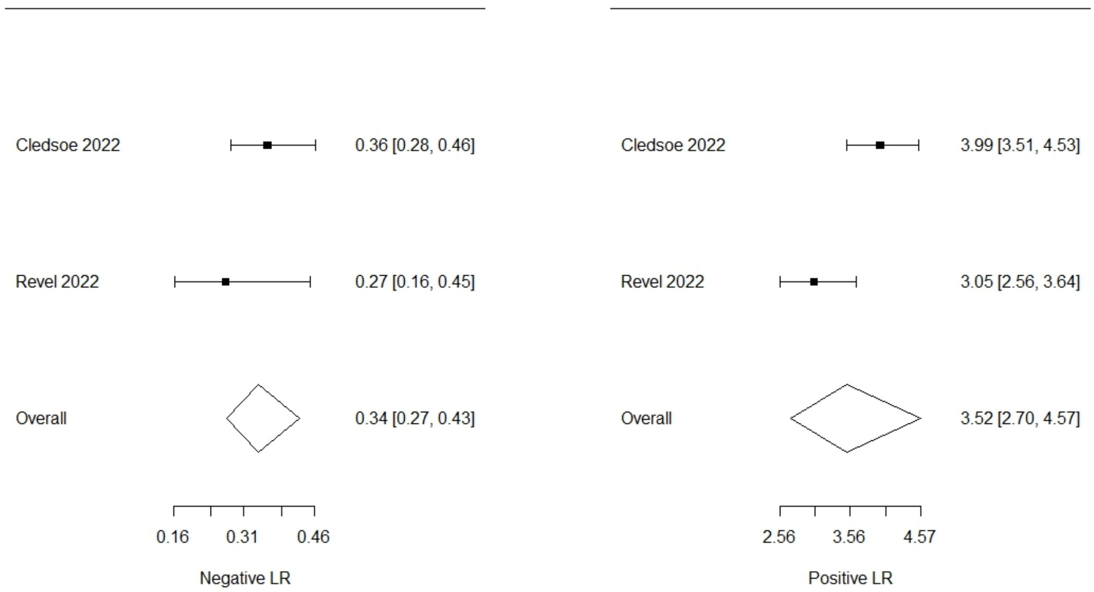
I^2 (negative LR) = 0%, I^2 positive LR = 54.6%

Figure 6:Sensitivity and Specificity for D-dimer with a threshold of 2000ng/ml (no Wells score) for pulmonary embolism (random effects)



I^2 (sensitivity) = 50.7%, I^2 specificity = 96.4%

Figure 7: Likelihood ratios for D-dimer with a threshold of 2000ng/ml (no Wells score) for pulmonary embolism (random effects)



I^2 (negative LR) = 0%, I^2 positive LR = 82.9%

Appendix F: GRADE

Table 10 D-dimer tests with standard cut-offs for pulmonary embolism in COVID-19

No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95%CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Wells score <6 plus D-dimer threshold 500ng/ml										
1 (Silva 2021)	Cross-sectional	300	95.7 (85.2 to 99.5)	8.3 (5.19 to 12.4)	LR+ 1.04 (0.97 to 1.12)	No serious	N/A	No serious	Serious[1]	Moderate
					LR- 0.53 (0.13 to 2.17)	No serious	N/A	No serious	Very serious[2]	Low
D-dimer with a threshold of 500ng/ml (no Wells score)										
9	Retrospective diagnostic accuracy	6245	96 (93 to 98)	14 (8 to 24)	LR+ 1.13 (1.04 to 1.26)	Very serious[3]	Very serious[4]	No serious	No serious	Very low
					LR- 0.28 (0.11 to 0.57)	Very serious[3]	Serious[5]	No serious	Serious[1]	Very low
Age-adjusted D-dimer (no Wells score)										
2	Retrospective diagnostic accuracy	606	90.5 (79.1 to 96)	27.4 (14.9 to 44.7)	LR+ 1.264 (1.007 to 1.586)	Very serious[6]	Serious[5]	No serious	No serious	Very low
					LR- 0.317 (0.135 to 0.743)	Very serious[6]	No serious	No serious	Serious[1]	Very low

1. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)
2. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) and (0.5,1)
3. All studies were retrospective, and the majority were rated moderate to high risk of bias.
4. I^2>66.7%
5. I^2>33.3%
6. Retrospective studies where it was not possible to determine if index test and reference standard tests were interpreted independently and risk of selection bias (non-consecutive enrolment) in one study.

Table 11 D-dimer tests with higher cut-offs for pulmonary embolism in COVID-19

No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95%CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Wells score <2.5 plus a D-dimer threshold of 4300ng/ml										
1 (Quezada-Feijoo 2021)	Cross-sectional	50	35.3 (17.3 to 58.7)	97 (84.7 to 99.5)	LR+ 11.65 (1.52 to 89.09)	Very serious[1]	N/A	No serious	Serious[2]	Very low
					LR- 0.67 (0.47 to 0.95)	Very serious[1]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 632 ng/ml (no Wells score)										
1 (Cerda 2020)	Cross-sectional	92	89.7 (73.6 to 96.4)	52.4 (40.3 to 64.2)	LR+ 1.88 (1.41 to 2.51)	Serious[3]	N/A	No serious	Serious[2]	Low
					LR- 0.20 (0.07 to 0.59)	Serious[3]	N/A	No serious	Serious[2]	Low
D-dimer threshold of 1000ng/ml (no Wells score)										
1 (Quezada-Feijoo 2021)	Cross-sectional	50	97.2 (67.8 to 99.8)	30.9 (17.8 to 48)	LR+ 1.41 (1.11 to 1.78)	Very serious[1]	N/A	No serious	No serious	Low
					LR- 0.09 (0.01 to 1.45)	Very serious[1]	N/A	No serious	Very serious[4]	Very low
D-dimer threshold of 1500ng/ml (no Wells score)										
1 (Raj 2021)	Retrospective cohort	109	80.8 (62.1 to 91.5)	85.5 (76.4 to 91.5)	LR+ 5.59 (3.20 to 9.74)	Very serious[1]	N/A	No serious	No serious	Low

					LR- 0.22 (0.10 to 0.50)	Very serious[1]	N/A	No serious	No serious	Low
D-dimer threshold of 2000ng/ml (no Wells score)										
2	Retrospective cohort	4634	74 (64 to 82)	78 (69 to 86)	LR+ 3.52 (2.70 to 4.57)	Very serious[5]	Very serious[8]	No serious	No serious	Very low
					LR- 0.34 (0.27 to 0.43)	Very serious[5]	No serious	No serious	No serious	Low
D-dimer threshold of 2281 ng/ml (no Wells score)										
1 (Estrada 2022)	Cross-sectional	209	60.0 (53.4 to 66.6)	76.9 (70.9 to 82.4)	LR+2.57 (2.1 to 3.14)	Very serious[6]	N/A	No serious	No serious	Low
					LR-0.52 (0.42 to 0.65)	Very serious[6]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 2454 ng/ml (no Wells score)										
1 (Polo Friz 2020)	Cross-sectional	41	63 (24 to 91)	73 (54 to 87)	LR+ 2.29 (1.06 to 4.97)	Very serious[7]	N/A	No serious	Serious[2]	Very low
					LR- 0.52 (0.21 to 1.29)	Very serious[7]	N/A	No serious	Very serious[4]	Very low
D-dimer threshold of 2495 ng/ml (no Wells score)										
1 (Nadeem 2021)	Cross-sectional	193	98.5 (80.4 to 99.9)	90.4 (84.8 to 94.1)	LR+ 10.23 (6.37 to 16.46)	Very serious[6]	N/A	No serious	No serious	Low
					LR- 0.02 (0.001 to 0.26)	Very serious[6]	N/A	No serious	No serious	Low

D-dimer threshold of 2590 ng/ml (no Wells score)										
1 (Mouhat 2020)	Cross-sectional	162	83.3 (68.6 to 93)	83.8 (3.8 to 91.1)	LR+ 5.22 (3.39 to 8.04)	Serious[3]	N/A	No serious	No serious	Moderate
					LR- 0.19 (0.10 to 0.38)	Serious[3]	N/A	No serious	No serious	Moderate
D-dimer threshold of 2660 ng/ml (no Wells score)										
1 (Leonard-Lorant 2020)	Cross-sectional	106	99 (80 to 100)	67.6 (56.3 to 77.1)	LR+ 3.02 (2.173 to 4.184)	Very serious[7]	N/A	No serious	No serious	Low
					LR- 0.023 (0.001 to 0.354)	Very serious[7]	N/A	No serious	No serious	Low
D-dimer threshold of 2903 ng/ml (no Wells score)										
1 (Ventura Diaz 2020)	Cross-sectional	242	80.8 (70.3 to 88.2)	59.2 (51.6 to 66.3)	LR+ 1.98 (1.6 to 2.45)	Very serious[7]	N/A	No serious	Serious[2]	Very low
					LR- 0.32 (0.2 to 0.53)	Very serious[7]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 4800 ng/ml (no Wells score)										
1 (Whyte 2020)	Retrospective cohort	214	75.0 (64.5 to 83.2)	78.4 (70.6 to 84.5)	LR+ 3.47 (2.45 to 4.9)	Very serious[6]	N/A	No serious	No serious	Low
					LR- 0.32 (0.22 to 0.47)	Very serious[6]	N/A	No serious	No serious	Low

1. Retrospective study where it was not possible to determine if index test and reference standard tests were interpreted independently and risk of selection bias (non-consecutive enrolment).
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)

3. Retrospective study where D-dimer cut off calculated from analysis.
4. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) and (0.5,1)
5. Retrospective studies where it was not possible to determine if index test and reference standard tests were interpreted independently. Risk of selection bias (non-consecutive enrolment) in one study. D-dimer cut-off based on exploratory analysis in one study.
6. Retrospective study where it was not possible to determine if index test and reference standard tests were interpreted independently and risk of selection bias (non-consecutive enrolment). D-dimer cut off calculated from analysis.
7. Retrospective study where it was not possible to determine if index test and reference standard tests were interpreted independently. D-dimer cut off calculated from analysis.
8. I^2> 66.7%

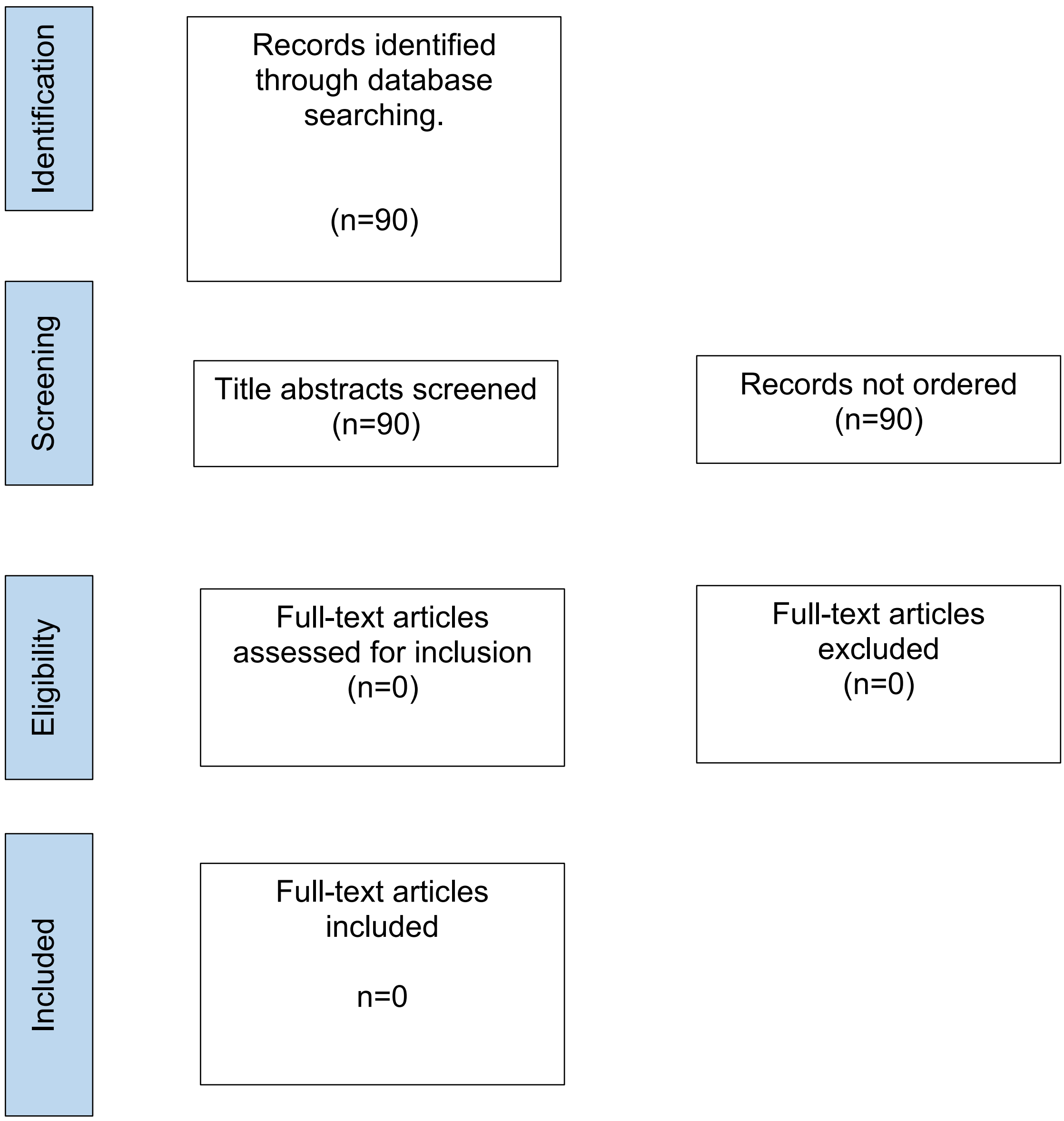
Table 12 D-dimer tests for deep vein thrombosis in COVID-19

No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95%CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
D-dimer threshold of 500ng/ml (no Wells score)										
1 (Raj 2021)	Retrospective cohort	106	94.3 (81.4 to 98.4)	29.6 (20.2 to 41)	LR+ 1.34 (1.13 to 1.59)	Very serious[1]	N/A	No serious	No serious	Low
					LR- 0.19 (0.05 to 0.78)	Very serious[1]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 1500ng/ml (no Wells score)										
1 (Raj 2021)	Retrospective cohort	106	74.3 (57.9 to 85.8)	77.5 (66.5 to 85.6)	LR+ 3.3 (2.05 to 5.29)	Very serious[1]	N/A	No serious	No serious	Low
					LR- 0.33 (0.19 to 0.59)	Very serious[1]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 2000ng/ml (no Wells score)										

1 (Trigonis 2020)	Cross-sectional	106	94.7 (75.4 to 99.1)	46.2 (28.8 to 64.5)	LR+ 1.76 (1.21 to 2.55)	Very serious[1]	N/A	No serious	Serious[2]	Very low
					LR- 0.11 (0.02 to 0.8)	Very serious[1]	N/A	No serious	Serious[2]	Very low
D-dimer threshold of 3000ng/ml (no Wells score)										
1 (Gibson 2020)	Retrospective cohort	72	96.2 (59.7 to 99.8)	51.6 (39.3 to 63.8)	LR+ 1.99 (1.50 to 2.63)	Very serious[3]	N/A	No serious	Serious[2]	Very low
					LR- 0.07 (0.01 to 1.14)	Very serious[3]	N/A	No serious	Very serious[4]	Very low
D-dimer threshold of 6494ng/ml (no Wells score)										
1 (Cho 2020)	Retrospective cohort	158	80.8 (68.1 to 89.2)	68.9 (59.5 to 76.9)	LR+ 2.59 (1.9 to 3.55)	Very serious[3]	N/A	No serious	Serious[2]	Very low
					LR- 0.28 (0.16 to 0.49)	Very serious[3]	N/A	No serious	No serious	Low

1. Retrospective study where it was not possible to determine if index test and reference standard tests were interpreted independently and risk of selection bias (non-consecutive enrolment).
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)
3. Retrospective study where it was not possible to determine if index test and reference standard tests were interpreted independently and risk of selection bias (non-consecutive enrolment). D-dimer cut off calculated from analysis.
4. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) and (0.5,1).

Appendix G: Economic evidence study selection



Appendix H: Economic evidence tables

No evidence identified.

Appendix I: Health economic model

Though this question was not prioritised for economic evaluation, an exploratory analysis of downstream costs was conducted.

The decision tree in Figure 8 was used to estimate economic consequences associated with D-dimer testing outcomes. Testing outcomes for standard threshold D-dimer tests (i.e. 500ng/ml) were compared to higher D-dimer thresholds for PE and for DVT.

A full cost-utility analysis would quantify all downstream costs and QALYs for each testing outcome in order to explicitly weigh up the trade-off between sensitivity and specificity in point-of-care tests. While consequences of false negatives are severe, these are not quantified here due to lack of necessary evidence on the rate of downstream outcomes and their associated costs and impact to patients.

All results of the calculations are only exploratory due to the lack of high quality and generalisable evidence to this review question.

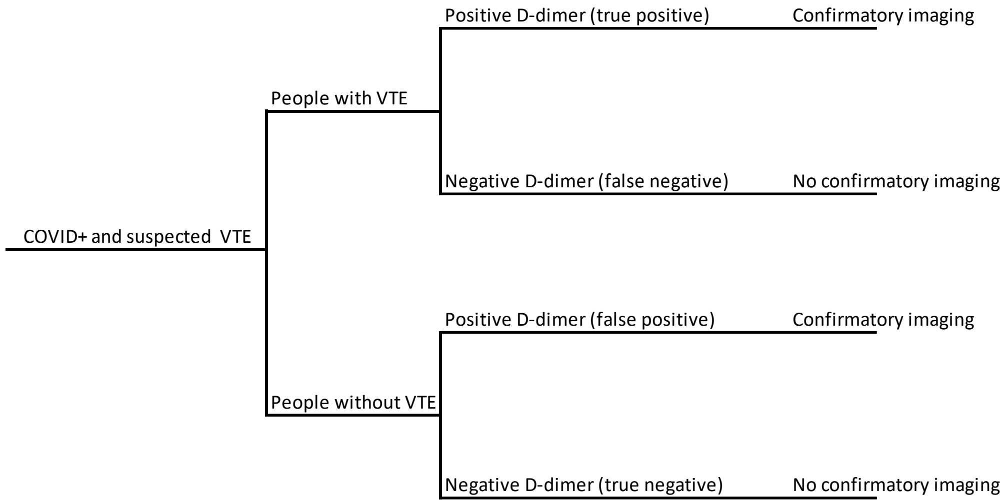


Figure 8: Decision tree structure

Data to calculate outcome rates were taken from the clinical review (specificity and sensitivity), as well as from studies estimating the rate of VTE events in hospitalised COVID-19 patients.

Epidemiology

Studies estimating VTE incidence identified in the literature are largely based on early COVID populations prior to vaccination and more severe disease, and therefore were not considered generalisable to the population at present. In particular, for the rate of PE and DVT in COVID patients, the studies identified were mostly based on early COVID populations admitted to hospital prior to vaccination and with more severe disease. In particular, the meta-analysis by Malas et al. (2020) found a 13% (95% CI: 11–16%) pooled rate of PE events in COVID-19 patients, and a 20% (95% CI: 13–28%) pooled rate of DVT events; and the meta-analysis by Jimenez et al. (2021) found pooled PE rate of 7.1% (95% CI, 5.3-9.1) and a pooled DVT rate of 12.1% (95% CI, 8.4-16.4) in COVID-19 patients.

In a retrospective exploratory analysis of UK Hospital Episode Statistics data, Roberts et al. (2022) found that VTE was diagnosed in 4.6% of patients hospitalised for COVID-19 between 1st March 2020 and 31st March 2021. However, given that the committee estimated a 2% incidence rate in the current post-omicron vaccinated population, data for this analysis was extracted from a Norwegian study, Tholin et al. (2021), which found an incidence rate of 3.9% (95% CI: 2.1–7.2) of VTE following hospitalisation for COVID up until June 2020.

Source	**Incidence rate VTE**	
Tholin et al. (2021)	3.9% (95% CI: 2.1–7.2)	
Roberts et al. (2022)	4.6% (CI not reported)	
Source	**Incidence rate PE**	**Incidence rate DVT**
Jimenez et al. (2021)	7.1% (95% CI, 5.3-9.1)	12.1% (95% CI, 8.4-16.4)
Malas et al. (2020)	13% (95% CI: 11–16%)	12.1% (95% CI, 8.4-16.4)

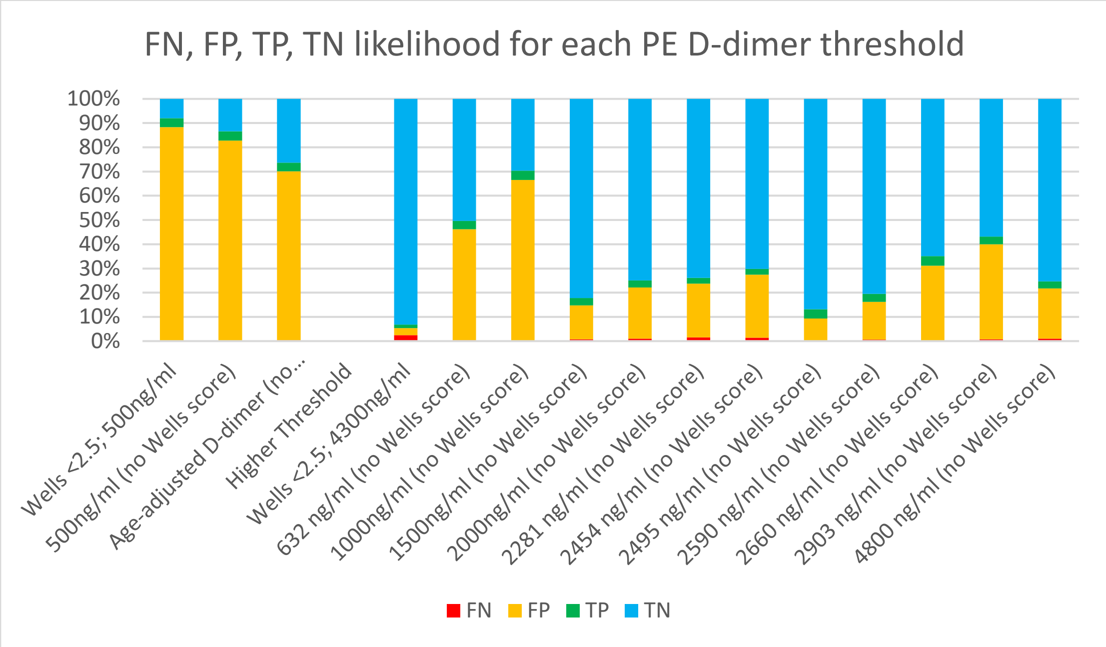
According to UK Coronavirus data, the number of hospitalised COVID adult patients in England for the last 3 months (at 27 February 2023) is 72,670.

Testing outcomes

Sensitivity and specificity inputs are considered to be uncertain given the low quality and non-generalisability of studies, which has been discussed at length in Section 2.1.12 of the evidence review.

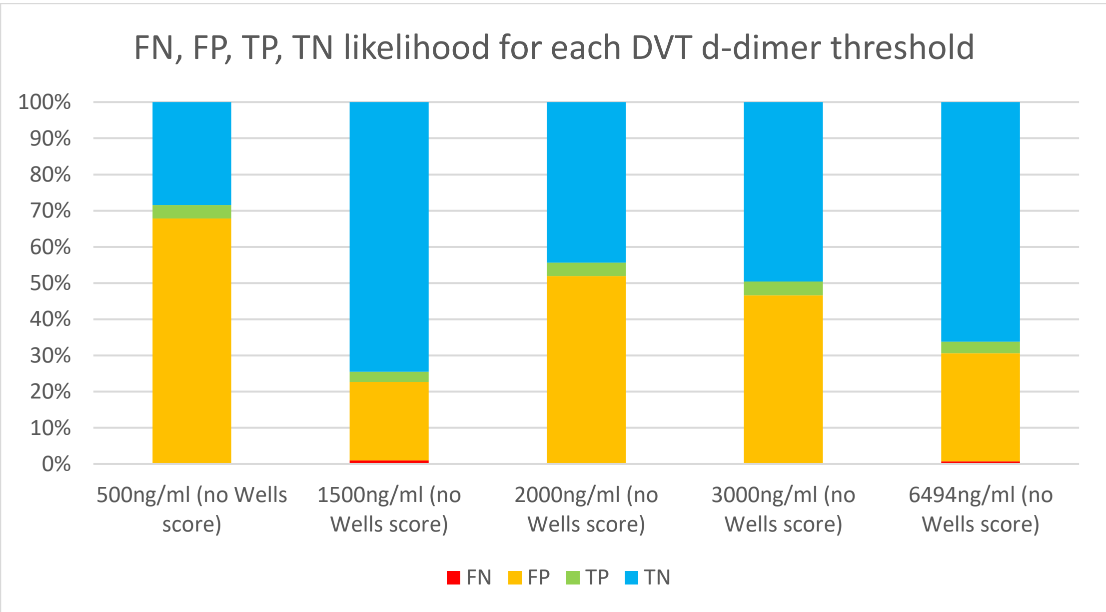
Currently, NICE recommends the use of age-adjusted D-dimer thresholds for people over 50 years of age. A threshold of 500ng/ml is otherwise typically used.

Figure 9: Testing outcomes for each Pulmonary Embolism (PE) D-Dimer threshold



A comparison of testing outcomes for PE according to D-dimer threshold is demonstrated graphically in Figure 9. Though there are some exceptions due to the uncertainty of the data, in general, false positive rates are decreased by increasing the D-dimer threshold. Similarly, false negatives generally increase with increasing thresholds.

Figure 10: Testing outcomes for each Pulmonary Embolism (PE) D-Dimer threshold



Similarly in Figure 10, a comparison of testing outcomes for DVT according to D-dimer threshold shows that false positive rates are decreased by increasing the D-dimer threshold, and that false negatives generally increase with increasing thresholds.

Higher false negative rates for higher thresholds are demonstrated more clearly in tables 14 and 15:

Table 13: PE D-Dimer false negatives per threshold

	Threshold	Rate of False Negatives
Standard D-Dimer thresholds (PE) used in current practice	Wells <2.5; 500ng/ml	0.17%
	500ng/ml (no Wells score)	0.16%
	Age-adjusted D-dimer (no Wells score)	0.37%
Higher D-Dimer thresholds (PE)	Wells <2.5; 4300ng/ml	2.52%
	632 ng/ml (no Wells score)	0.40%
	1000ng/ml (no Wells score)	0.11%
	1500ng/ml (no Wells score)	0.75%
	2000ng/ml (no Wells score)	1.01%
	2281 ng/ml (no Wells score)	1.56%
	2454 ng/ml (no Wells score)	1.44%
	2495 ng/ml (no Wells score)	0.06%
	2590 ng/ml (no Wells score)	0.65%
	2660 ng/ml (no Wells score)	0.04%
	2903 ng/ml (no Wells score)	0.75%
	4800 ng/ml (no Wells score)	0.98%

Table 14: DVT D-Dimer false negatives per threshold

	Threshold	Rate of False Negatives
Standard D-Dimer threshold (DVT) used in current practice	500ng/ml (no Wells score)	0.22%
Higher D-Dimer thresholds (DVT)	1500ng/ml (no Wells score)	1.00%
	2000ng/ml (no Wells score)	0.21%
	3000ng/ml (no Wells score)	0.15%
	6494ng/ml (no Wells score)	0.75%

Costs of imaging

It was assumed that all D-dimer testing was carried out in the hospital laboratory and that there would be no difference in D-dimer costs across arms, and so these costs were excluded from the analysis. Anticoagulation costs were also excluded from the analysis. The committee advised that all COVID-19 patients with suspected VTE would receive this prophylactic anti-coagulation treatment, regardless of the outcome of their D-dimer test.

To estimate indicative costs from false positive tests for pulmonary embolism (PE), it was assumed that 95% of patients would receive computed tomography pulmonary angiograms (CTPA scans), and 5% would receive ventilation/perfusion (V/Q) scans in cases of intolerance to the contrast used for CTPA scans. The cost of one unit of PE imaging was calculated to be £89.74 based on a weighted cost of each scan from the 2019/20 NHS Cost Collection dataset. Patients who have a positive test for DVT incur the cost of a vascular ultrasound scan.

Table 15: Cost details

	Cost	Source

Imaging PE		
Computerised Tomography (CTPA) Scan of One Area, with Post-Contrast Only, 19 years and over	£79.96	NHS Reference Costs 2019/20 v2, Total HRGs
Lung Ventilation or Perfusion (V/Q) Scan, 19 years and over	£275.51	NHS Reference Costs 2019/20 v2, Total HRGs
Proportion of patients who receive CTPA	0.95	Committee assumption
Proportion of patients who receive V/Q scan	0.05	Committee assumption
Imaging DVT		
Vascular Ultrasound Scan	£68.55	NHS Reference Costs 2019/20 v2, Total HRGs Tab

Results

For a hypothetical cohort of 1000 patients, it was found that retaining the standard D-dimer threshold instead of using a higher threshold would produce on average between 138 and 773 additional false positive test results for PE, resulting in additional costs of imaging of between £12,361 and £69,368.

Table 16: Pulmonary embolism: Cost savings from averted false positives

Threshold	False positives in 1000 patients	Average false positives averted[1] in 1000 patient cohort	Savings from false positives averted in a 1000 patient cohort
D-dimer thresholds used in current practice			

Wells <2.5; 500ng/ml	881		
500ng/ml (no Wells score)	826		
Age-adjusted D-dimer (no Wells score)	698		
Average for standard threshold	802		
Higher D-dimer thresholds			
Wells <2.5; 4300ng/ml	29	773	£69,367.59
632 ng/ml (no Wells score)	457	344	£30,903.51
1000ng/ml (no Wells score)	664	138	£12,361.40
1500ng/ml (no Wells score)	139	662	£59,449.72
2000ng/ml (no Wells score)	211	590	£52,981.55
2281 ng/ml (no Wells score)	222	580	£52,032.88
2454 ng/ml (no Wells score)	259	542	£48,669.43
2495 ng/ml (no Wells score)	92	710	£63,675.60
2590 ng/ml (no Wells score)	156	646	£57,983.60
2660 ng/ml (no Wells score)	311	490	£44,012.34
2903 ng/ml (no Wells score)	392	410	£36,767.99
4800 ng/ml (no Wells score)	208	594	£53,326.52

[1]Caculated by subtracting false positives from each higher threshold from the false positive outcome for the average standard threshold.

For deep vein thrombosis (DVT), remaining with the existing D-dimer threshold instead of using a higher threshold would estimate on average between 160 and 460 additional false positive test, resulting in additional costs of confirmatory imaging of between £10,936 and £31,555.

Table 17: DVT: Cost savings from false positives averted

Threshold	False Positives in 1000 patients	False positives averted in 1000 patient cohort	Savings from false positives averted in a 1000 patient cohort
D-dimer thresholds used in current practice			
500ng/ml (no Wells score)	677		
Higher D-dimer thresholds			
1500ng/ml (no Wells score)	216	460	£31,554.87
2000ng/ml (no Wells score)	517	160	£10,935.51
3000ng/ml (no Wells score)	465	211	£14,492.84
6494ng/ml (no Wells score)	299	378	£25,889.48

Considering the COVID-19 hospitalised population over the last 3 months, if it is assumed that the prevalence of VTE in the COVID population is 3.9% (Tholin et al. 2021), the cost impact of confirmatory testing was estimated to be between £35,034 and £196,597 for PE, and between £41,075 and £89,431 for DVT, for the existing D-dimer threshold compared with using a higher threshold. If another scenario is tested in which the prevalence of VTE in the COVID population is 2% as per the committee's assumption, the cost impact of confirmatory testing is estimated to be between £17,966 and £100,819 for PE, and between £15,894 and £45,862 for DVT, for the existing D-dimer threshold compared with using a higher threshold.

Appendix J: Excluded studies

Table 18 Studies excluded from the evidence reviews

Study	Reason for exclusion
Ahlers, P. and Said-Hartley, M.Q. (2022) A retrospective review of CT pulmonary angiogram confirmed pulmonary emboli in COVID-19 patients admitted to Groote Schuur Hospital, Cape Town. South African Journal of Radiology 26(1): a2280	CTPA for diagnosis of COVID-19 not for diagnosis of PE Not a DTA study
Al-Samkari, Hanny, Karp Leaf, Rebecca S, Dzik, Walter H et al. (2020) COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 136(4): 489-500	Not a DTA study
Al-Samkari, Hanny, Song, Fei, Van Cott, Elizabeth M et al. (2020) Evaluation of the prothrombin fragment 1.2 in patients with coronavirus disease 2019 (COVID-19). American journal of hematology 95(12): 1479-1485	Not a DTA study
Alonso-Fernandez, Alberto, Toledo-Pons, Nuria, Cosio, Borja G et al. (2020) Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. PloS one 15(8): e0238216	D-dimer used to determine if reference standard applied Only those with D-dimer >1 µg/mL underwent computed tomography pulmonary angiography (CTPA)
Alshami, A., Grzybacz, D., Pozdniakova, H. et al. (2022) Redefining the Wells criteria for pulmonary embolism to include Covid-19. Critical Care and Shock 25(6): 279-282	Non-systematic review
Alvarez-Troncoso, Jorge, Ramos-Ruperto, Luis, Fernandez-Cidon, Pelayo et al. (2022) Screening Protocol and Prevalence of Venous Thromboembolic Disease in Hospitalized Patients With COVID-19. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 41(7): 1689-1698	D-dimer used to determine if reference standard applied The inclusion criteria were adult patients older than 18 years diagnosed with COVID-19 who presented an elevated age-adjusted D-dimer, regardless of the presence or absence of symptoms of DVT or PE.
Artifoni, Mathieu, Danic, Gwenvael, Gautier, Giovanni et al. (2020) Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. Journal of thrombosis and thrombolysis 50(1): 211-216	Not all received index test
Barnes, Drew H, Lo, Kevin Bryan, Bhargav, Ruchika et al. (2021) Predictors of venous thromboembolism in patients with COVID-19 in an underserved urban population: A single tertiary center experience. The clinical respiratory journal 15(8): 885-891	Not a DTA study
Bellmunt-Montoya, Sergi, Riera, Claudia, Gil, Daniel et al. (2021) COVID-19 Infection in Critically Ill Patients Carries a High Risk of Venous Thrombo-embolism. European journal of vascular and endovascular	Not a DTA study

surgery : the official journal of the European Society for Vascular Surgery 61(4): 628-634	
Betoule, Anna, Martinet, Camille, Gasperini, Guillaume et al. (2020) Diagnosis of venous and arterial thromboembolic events in COVID-19 virus-infected patients. Journal of thrombosis and thrombolysis 50(2): 302-304	Not a DTA study
Bompard F, Monnier H, Saab I et al. (2020) Pulmonary embolism in patients with COVID-19 pneumonia. The European respiratory journal 56(1)	Prevalence of VTE
Cau, Riccardo, Pacielli, Alberto, Fatemeh, Homayounieh et al. (2021) Complications in COVID-19 patients: Characteristics of pulmonary embolism. Clinical imaging 77: 244-249	No information on index test
Cerdà, Pau, Ribas, Jesus, Iriarte, Adriana et al. (2020) D-dimer dynamics in hospitalized COVID-19 patients: potential utility for diagnosis of pulmonary embolism.	Pre-print of published study
Costa, Alessandro, Weinstein, Eric S, Sahoo, D Ruby et al. (2020) How to Build the Plane While Flying: VTE/PE Thromboprophylaxis Clinical Guidelines for COVID-19 Patients. Disaster medicine and public health preparedness 14(3): 391-405	Thromboprophylaxis
Creel-Bulos, Christina, Liu, Michael, Auld, Sara C et al. (2020) Trends and diagnostic value of D-dimer levels in patients hospitalized with coronavirus disease 2019. Medicine 99(46): e23186	Not all or unclear if all received reference standard
Cui, Songping, Chen, Shuo, Li, Xiunan et al. (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH 18(6): 1421-1424	Not a DTA study Unclear how D-dimer cut offs were determined.
Das, Jeeban P; Yeh, Randy; Schoder, Heiko (2021) Clinical utility of perfusion (Q)-single-photon emission computed tomography (SPECT)/CT for diagnosing pulmonary embolus (PE) in COVID-19 patients with a moderate to high pre-test probability of PE. European journal of nuclear medicine and molecular imaging 48(3): 794-799	D-dimer not index test
de Godoy, J.M.P., da Silva, M.O.M., Amorim Santos, H. et al. (2022) Mortality, deep vein thrombosis, and D-dimer levels in patients with COVID-19. Cor et Vasa 64(4): 399-402	Association of D-dimer with mortality
Demelo-Rodriguez, P, Cervilla-Munoz, E, Ordieres-Ortega, L et al. (2020) Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thrombosis research 192: 23-26	D-dimer used to determine if reference standard applied Patients were included in the study if D-dimer levels were higher than 1000 ng/ml
Dubois-Silva, Álvaro, Barbagelata-López, Cristina, Mena, Álvaro et al. (2020) Pulmonary embolism and screening for concomitant proximal deep vein thrombosis in noncritically ill hospitalized patients with coronavirus disease 2019.	Confirmed VTE diagnosis Inclusion criteria was confirmed PE diagnosis
El-Qutob, D, Alvarez-Arroyo, L, Barreda, I et al. (2022) High incidence of pulmonary thromboembolism in hospitalized SARS-CoV-2 infected patients despite thrombo-prophylaxis. Heart & lung : the journal of critical care 53: 77-82	Prevalence of VTE

Espallargas, Irene, Rodriguez Sevilla, Juan Jose, Rodriguez Chiaradia, Diego Agustin et al. (2021) CT imaging of pulmonary embolism in patients with COVID-19 pneumonia: a retrospective analysis. European radiology 31(4): 1915-1922	D-dimer not index test
Fang, C, Garzillo, G, Batohi, B et al. (2020) Extent of pulmonary thromboembolic disease in patients with COVID-19 on CT: relationship with pulmonary parenchymal disease. Clinical radiology 75(10): 780-788	Unable to extract 2x2 data
Fraissé M, Logre E, Pajot O et al. (2020) Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Critical care (London, England) 24(1): 275	Not a DTA study
Franco-Moreno, A.I., Bustamante-Fermosel, A., Ruiz-Giardin, J.M. et al. (2022) Utility of probability scores for the diagnosis of pulmonary embolism in patients with SARS-CoV-2 infection: A systematic review. Revista Clinica Espanola	Systematic review broader than scope Includes different probability scores. Used as a source of references
Franco-Moreno, A, Brown-Lavalle, D, Rodríguez-Ramírez, N et al. (2022) Clinical prediction model for pulmonary embolism diagnosis in hospitalized patients with SARS-CoV-2 infection.	Different pretest probability score used CHEDDAR score
FRIZ, Hernan POLO, GELFI, Elia, ORENTI, Annalisa et al. (2020) Acute pulmonary embolism in patients presenting pulmonary deterioration after admission to internal medicine wards for non-critical COVID-19.	Pre-print of published study
Galland, Joris, Thoreau, Benjamin, Delrue, Maxime et al. (2021) White blood count, D-dimers, and ferritin levels as predictive factors of pulmonary embolism suspected upon admission in noncritically ill COVID-19 patients: The French multicenter CLOTVID retrospective study. European journal of haematology 107(2): 190-201	D-dimer as a risk factor or predictive factor Not used for diagnosis
Garcia-Cervera, Carles, Giner-Galvan, Vicente, Wikman-Jorgensen, Philip et al. (2021) Estimation of Admission D-dimer Cut-off Value to Predict Venous Thrombotic Events in Hospitalized COVID-19 Patients: Analysis of the SEMI-COVID-19 Registry. Journal of general internal medicine 36(11): 3478-3486	No information on reference standard
Garcia-Olive, Ignasi, Sintes, Helena, Radua, Joaquim et al. (2020) D-dimer in patients infected with COVID-19 and suspected pulmonary embolism. Respiratory medicine 169: 106023	Not a DTA study
Garcia-Olive, Ignasi, Sintes, Helena, Radua, Joaquim et al. (2021) Predicting pulmonary embolism in patients infected with COVID-19 based on D-dimer levels and days between diagnosis of the infection and D-dimer determination. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 91(2)	Population included those without VTE suspicion
Gervaise, Alban, Bouzad, Caroline, Peroux, Evelyne et al. (2020) Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. European radiology 30(11): 6170-6177	Prevalence of VTE
Grandmaison G, Andrey A, Périard D et al. (2020) Systematic Screening for Venous Thromboembolic	Screening for VTE

Events in COVID-19 Pneumonia. TH open : companion journal to thrombosis and haemostasis 4(2): e113-e115	
Hékimian G, Lebreton G, Bréchot N et al. (2020) Severe pulmonary embolism in COVID-19 patients: a call for increased awareness. Critical care (London, England) 24(1): 274	Not a DTA study
Ippolito, Davide, Capodaglio, Carlo, Maino, Cesare et al. (2022) Compressive ultrasound can predict early pulmonary embolism onset in COVID patients. Journal of ultrasound 25(3): 571-577	D-dimer not index test
Kalyanasundaram, S., Sudarsanam, H., Dhas, D. et al. (2022) Role of Combined CT Pulmonary Angiography and Indirect CT Venography in Diagnosing Venous Thromboembolism in COVID-19 Patients - Experience From an Indian Quaternary Centre. Vascular and Endovascular Surgery	D-dimer not index test
Kaminetzky M, Moore W, Fansiwala K et al. (2020) Pulmonary Embolism at CT Pulmonary Angiography in Patients with COVID-19. Radiology. Cardiothoracic imaging 2(4): e200308	Not all received index test
Kampouri, Eleftheria, Filippidis, Paraskevas, Viala, Benjamin et al. (2020) Predicting Venous Thromboembolic Events in Patients with Coronavirus Disease 2019 Requiring Hospitalization: an Observational Retrospective Study by the COVIDIC Initiative in a Swiss University Hospital. BioMed research international 2020: 9126148	Not all or unclear if all received reference standard
Kartsios, Charalampos, Lokare, Anand, Osman, Husam et al. (2021) Diagnosis, management, and outcomes of venous thromboembolism in COVID-19 positive patients: a role for direct anticoagulants?. Journal of thrombosis and thrombolysis 51(4): 947-952	Not a DTA study
Khan, Muhammad Ziaullah, Jamal, Yousaf, Sutton, Benjamin et al. (2020) Venous thromboembolism in patients with COVID-19 and correlation with D-dimers: a single-centre experience. BMJ open respiratory research 7(1)	Not all or unclear if all received reference standard
Khider, L., Soudet, S., Laneelle, D. et al. (2020) Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in outpatients with COVID-19. JMV-Journal de Medecine Vasculaire 45(4): 210-213	Guidance
Kirsch, Brittany, Aziz, Moez, Kumar, Sungita et al. (2021) Wells Score to Predict Pulmonary Embolism in Patients with Coronavirus Disease 2019. The American journal of medicine 134(5): 688-690	Wells Score only
Korevaar, Daniel A, Aydemir, Ilayda, Minnema, Maartje W et al. (2021) Routine screening for pulmonary embolism in COVID-19 patients at the emergency department: impact of D-dimer testing followed by CTPA. Journal of thrombosis and thrombolysis 52(4): 1068-1073	D-dimer used to determine if reference standard applied If D-dimer is ≥ 1.00 mg/L, CTPA is subsequently done.
Kutsogiannis, D.J., Alharthy, A., Balhamar, A. et al. (2022) Mortality and Pulmonary Embolism in Acute Respiratory Distress Syndrome From COVID-19 vs. Non-COVID-19. Frontiers in Medicine 9: 800241	Not a DTA study

Kwee, Robert M; Adams, Hugo J A; Kwee, Thomas C (2021) Pulmonary embolism in patients with COVID-19 and value of D-dimer assessment: a meta-analysis. European radiology 31(11): 8168-8186	Systematic review with older search date Used as source of references
Laouan Brem, Falmata, Asmae, Boudouh, Amane, Yassine et al. (2021) Diagnostic Accuracy of D-Dimers for Predicting Pulmonary Embolism in COVID-19-Patients. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 27: 10760296211057901	D-dimer used to determine if reference standard applied
Lee, Y., Jehangir, Q., Lin, C.-H. et al. (2022) 3D-PAST: Risk Assessment Model for Predicting Venous Thromboembolism in COVID-19. Journal of Clinical Medicine 11(14): 3949	Not a DTA study
Lehmann, Antje, Prosch, Helmut, Zehetmayer, Sonja et al. (2021) Impact of persistent D-dimer elevation following recovery from COVID-19. PloS one 16(10): e0258351	Not a DTA study
Lin, K., Xu, K., Daoust, R. et al. (2022) DIAGNOSTIC ACCURACY OF AGE-ADJUSTED D-DIMER FOR PULMONARY EMBOLISM AMONG EMERGENCY DEPARTMENT PATIENTS WITH SUSPECTED SARS-COV-2: A CANADIAN COVID-19 EMERGENCY DEPARTMENT RAPID RESPONSE NETWORK STUDY. medRxiv	Unable to extract 2x2 data Number of people with confirmed PE not reported
Loffi, Marco, Regazzoni, Valentina, Toselli, Marco et al. (2021) Incidence and characterization of acute pulmonary embolism in patients with SARS-CoV-2 pneumonia: A multicenter Italian experience. PloS one 16(1): e0245565	D-dimer not index test D-dimer used to determine if reference standard applied CPTA carried out if D-dimer levels were high
Maatman, Thomas K, Jalali, Farid, Feizpour, Cyrus et al. (2020) Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019. Critical care medicine 48(9): e783-e790	Thromboprophylaxis
Machowski, M., Polanska, A., Galecka-Nowak, M. et al. (2022) Age-Adjusted D-Dimer Levels May Improve Diagnostic Assessment for Pulmonary Embolism in COVID-19 Patients. Journal of Clinical Medicine 11(12): 3298	Not all or unclear if all received reference standard
Martens, E.S.L.; Huisman, M.V.; Klok, F.A. (2022) Diagnostic Management of Acute Pulmonary Embolism in COVID-19 and Other Special Patient Populations. Diagnostics 12(6): 1350	Non-systematic review
Masselli, Gabriele, Almberger, Maria, Tortora, Alessandra et al. (2021) Role of CT angiography in detecting acute pulmonary embolism associated with COVID-19 pneumonia. La Radiologia medica 126(12): 1553-1560	D-dimer not index test
Meisinger, Christa, Kirchberger, Inge, Warm, Tobias D et al. (2022) Elevated Plasma D-Dimer Concentrations in Adults after an Outpatient-Treated COVID-19 Infection. Viruses 14(11)	Not a DTA study
Mestre-Gomez, B, Lorente-Ramos, R M, Rogado, J et al. (2021) Incidence of pulmonary embolism in non-	D-dimer not index test

critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. Journal of thrombosis and thrombolysis 51(1): 40-46	Not a DTA study
Monfardini, Lorenzo, Morassi, Mauro, Botti, Paolo et al. (2020) Pulmonary thromboembolism in hospitalised COVID-19 patients at moderate to high risk by Wells score: a report from Lombardy, Italy. The British journal of radiology 93(1113): 20200407	Unable to extract 2x2 data
Naymagon, Leonard, Zubizarreta, Nicole, Feld, Jonathan et al. (2020) Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. Thrombosis research 196: 99-105	No information on reference standard
Obi, Andrea T, Barnes, Geoff D, Wakefield, Thomas W et al. (2020) Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. Journal of vascular surgery. Venous and lymphatic disorders 8(4): 526-534	Guidance
Ooi, M W X, Rajai, A, Patel, R et al. (2020) Pulmonary thromboembolic disease in COVID-19 patients on CT pulmonary angiography - Prevalence, pattern of disease and relationship to D-dimer. European journal of radiology 132: 109336	Not all received index test
Ozturk, Buket Caliskaner, Atahan, Ersan, Gencer, Aysegul et al. (2021) Investigation of perfusion defects by Q-SPECT/CT in patients with mild-to-moderate course of COVID-19 and low clinical probability for pulmonary embolism. Annals of nuclear medicine 35(10): 1117-1125	D-dimer used to determine if reference standard applied
Paz Rios, L.H., Minga, I., Kwak, E. et al. (2021) Prognostic Value of Venous Thromboembolism Risk Assessment Models in Patients with Severe COVID-19. TH Open 5(2): e211-e219	Not a DTA study
Perera, A., Chowdary, P., Johnson, J. et al. (2021) A 10-fold and greater increase in D-dimer at admission in COVID-19 patients is highly predictive of pulmonary embolism in a retrospective cohort study. Therapeutic Advances in Hematology 12	Not all received index test
Piazza, G. and Morrow, D.A. (2020) Diagnosis, management, and pathophysiology of arterial and venous thrombosis in covid-19. JAMA - Journal of the American Medical Association 324(24): 2548-2549	Not a DTA study
Planquette, Benjamin, Khider, Lina, Berre, Alice Le et al. (2022) Adjusting D-dimer to Lung Disease Extent to Exclude Pulmonary Embolism in COVID-19 Patients (Co-LEAD). Thrombosis and haemostasis 122(11): 1888-1898	Not all received index test
Poissy J, Goutay J, Caplan M et al. (2020) Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation 142(2): 184-186	CTPA for diagnosis of COVID-19 not for diagnosis of PE Not a DTA study
Ramadan L, Koziatek CA, Caldwell JR et al. (2021) Pulmonary thromboembolism in COVID-19: Evaluating the role of D-dimer and computed tomography pulmonary angiography results. The American journal of emergency medicine 46: 786-787	Unable to extract 2x2 data
Rindi, Lorenzo Vittorio, Al Moghazi, Samir, Donno, Davide Roberto et al. (2022) Predictive scores for the	Wells Score only

diagnosis of Pulmonary Embolism in COVID-19: A systematic review. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 115: 93-100	
Riyahi, Sadjad, Dev, Hreedi, Behzadi, Ashkan et al. (2021) Pulmonary Embolism in Hospitalized Patients with COVID-19: A Multicenter Study. Radiology 301(3): e426-e433	Not all received index test
Rodriguez-Leal, Cristobal Manuel, Garcia-Del-Salto, Laura, Coperias, Jose Luis et al. (2022) Usefulness of D-dimer concentration in the diagnosis of pulmonary thromboembolism in patients with COVID-19 in the emergency department: estimating its discriminative capacity, sensitivity, and specificity. Emergencias : revista de la Sociedad Espanola de Medicina de Emergencias 34(2): 150-152	Non-English language article
Rodriguez-Sevilla, J.J., Rodo-Pin, A., Espallargas, I. et al. (2020) Pulmonary Embolism in Patients With Covid-19 Pneumonia: The Utility of D-dimer. Archivos de Bronconeumologia 56(11): 758-759	D-dimer used to determine if reference standard applied CPTA indication included elevated D-dimers
Rosovsky, Rachel P, Grodzin, Charles, Channick, Richard et al. (2020) Diagnosis and Treatment of Pulmonary Embolism During the Coronavirus Disease 2019 Pandemic: A Position Paper From the National PERT Consortium. Chest 158(6): 2590-2601	Guidance
Rueda-Camino, Jose Antonio, Sendin-Martin, Vanesa, Joya-Seijo, Maria Dolores et al. (2022) Plasma D-dimer value corrected by inflammatory markers in patients with SARS-CoV-2 infection: Its prognostic value in the diagnosis of venous thromboembolism. Medicina clinica 158(6): 265-269	Not a DTA study
Saeed, G.A., Gaba, W.H., Adi, A.A.K. et al. (2021) Pulmonary thromboembolism in COVID-19 Patients on CT Pulmonary Angiography - A Single-Centre Retrospective Cohort Study in the United Arab Emirates. medRxiv	CTPA for diagnosis of COVID-19 not for diagnosis of PE
Schaarschmidt, B.M., Fistera, D., Li, Y. et al. (2022) Streamlining Patient Management of Suspected COVID-19 Patients in the Emergency Department: Incorporation of Pulmonary CT Angiography into the Triaging Algorithm. Diagnostics 12(5): 1183	D-dimer not index test
Schiaffino, Simone, Giacomazzi, Francesca, Esseridou, Anastassia et al. (2021) Pulmonary thromboembolism in coronavirus disease 2019 patients undergoing thromboprophylaxis. Medicine 100(1): e24002	D-dimer not index test
Sebuhyan, M, Mirailles, R, Crichi, B et al. (2020) How to screen and diagnose deep venous thrombosis (DVT) in patients hospitalized for or suspected of COVID-19 infection, outside the intensive care units. Journal de medecine vasculaire 45(6): 334-343	Non-systematic review
Stals, M.A.M., Kaptein, F.H.J., Bemelmans, R.H.H. et al. (2021) Ruling out Pulmonary Embolism in Patients with (Suspected) COVID-19-A Prospective Cohort Study. TH Open 5(3): e387-e399	Different pretest probability score used YEARS score
Stals, Mam, Kaptein, Fhj, Kroft, Ljm et al. (2021) Challenges in the diagnostic approach of suspected	Non-systematic review

pulmonary embolism in COVID-19 patients. Postgraduate medicine 133(sup1): 36-41	
Suarez Castillejo, C., Toledo-Pons, N., Calvo, N. et al. (2022) A Prospective Study Evaluating Cumulative Incidence and a Specific Prediction Rule in Pulmonary Embolism in COVID-19. Frontiers in Medicine 9: 936816	D-dimer not index test
Suh, Young Joo, Hong, Hyunsook, Ohana, Mickael et al. (2021) Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology 298(2): e70-e80	Systematic review broader than scope Used as source of references
Taccone, Fabio Silvio, Gevenois, Pierre Alain, Peluso, Lorenzo et al. (2020) Higher Intensity Thromboprophylaxis Regimens and Pulmonary Embolism in Critically Ill Coronavirus Disease 2019 Patients. Critical care medicine 48(11): e1087-e1090	Unclear how D-dimer cut offs were determined
Townsend, L., Fogarty, H., Dyer, A. et al. (2021) Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. Journal of Thrombosis and Haemostasis 19(4): 1064-1070	Not a DTA study
Tuck, Alexander A, White, Harriet L, Abdalla, Badr A et al. (2021) To scan or not to scan - D-dimers and computed tomography pulmonary angiography in the era of COVID-19. Clinical medicine (London, England) 21(2): e155-e160	Not a DTA study
Voicu, S, Delrue, M, Chousterman, B G et al. (2020) Imbalance between procoagulant factors and natural coagulation inhibitors contributes to hypercoagulability in the critically ill COVID-19 patient: clinical implications. European review for medical and pharmacological sciences 24(17): 9161-9168	Not all or unclear if all received reference standard
Wright, Franklin L, Vogler, Thomas O, Moore, Ernest E et al. (2020) Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. Journal of the American College of Surgeons 231(2): 193-203e1	Not a DTA study
Yu, Yuan, Tu, Jie, Lei, Bingxin et al. (2020) Incidence and Risk Factors of Deep Vein Thrombosis in Hospitalized COVID-19 Patients. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 26: 1076029620953217	Not a DTA study
Zhan, Haoting, Chen, Haizhen, Liu, Chenxi et al. (2021) Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 27: 10760296211010976	Systematic review with older search date Searched only until Sept 2020. Used as source of references
Zotzmann, Viviane, Lang, Corinna N, Wengenmayer, Tobias et al. (2021) Combining lung ultrasound and Wells score for diagnosing pulmonary embolism in critically ill COVID-19 patients. Journal of thrombosis and thrombolysis 52(1): 76-84	D-dimer not index test

Appendix K: Research recommendations – full details

K1.1 Research recommendation

No research recommendations were made by the committee.

Appendix L: Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2022 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Methods of combining evidence

Data synthesis for diagnostic accuracy data

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The ‘raw’ 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline were as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.

  LR+ = (TP/[TP+FN])/(FP/[FP+TN])

- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.

  LR- = (FN/[TP+FN])/(TN/[FP+TN])

- Sensitivity is the probability that the feature will be positive in a person with the condition.

  sensitivity = TP/(TP+FN)

- **Specificity** is the probability that the feature will be negative in a person without the condition.

  specificity = TN/(FP+TN)

Meta-analysis of diagnostic accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.1 (Deeks et al. 2022).

Where five or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using R. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Appraising the quality of evidence

Diagnostic accuracy studies

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies was initially rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 20: Rationale for downgrading quality of evidence for diagnostic accuracy databelow.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

Using likelihood ratios as the primary outcomes

The following schema (Table 20: Rationale for downgrading quality of evidence for diagnostic accuracy data), adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 19 Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

GRADE assessments were only undertaken for positive and negative likelihood ratios but results for sensitivity and specificity are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the likelihood ratio above (or below for negative likelihood ratios) which a test would be recommended, and a second below (or above for negative likelihood ratios) which a test would be considered of no clinical use. These were used to judge imprecision (see below). If the committee were unsure which values to pick, then the values of 2 for LR+ and 0.5 for LR- were used based on Table 19 Interpretation of likelihood ratios, with the line of no effect (being 1.0) as the second clinical decision line in both cases.

Table 20: Rationale for downgrading quality of evidence for diagnostic accuracy data

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I2 was less than 33.3%, the outcome was not downgraded. Serious: If the I2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If the 95% confidence interval for the outcome crossed one of the clinical decision thresholds, the outcome was downgraded one level. If the 95%

GRADE criteria	Reasons for downgrading quality
	confidence interval spanned both thresholds, the outcome was downgraded twice. See the sections on ‘Using sensitivity and specificity as the primary outcome’ and ‘Using likelihood ratios as the primary outcome’ for a description of how clinical decision thresholds were agreed.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Reviewing economic evidence

Inclusion and exclusion of economic studies

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Appraising the quality of economic evidence

Economic studies identified through a systematic search of the literature were appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 21.

Table 21 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 22.

Table 22 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.