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Pulmonary embolism in patients with COVID-19 and value of D-dimer assessment: a meta-analysis

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Abstract

Purpose To investigate, in a meta-analysis, the frequency of pulmonary embolism (PE) in patients with COVID-19 and whether D-dimer assessment may be useful to select patients for computed tomography pulmonary angiography (CTPA).

Methods A systematic literature search was performed for original studies which reported the frequency of PE on CTPA in patients with COVID-19. The frequency of PE, the location of PE, and the standardized mean difference (SMD) of D-dimer levels between patients with and without PE were pooled by random effects models.

Results Seventy-one studies were included. Pooled frequencies of PE in patients with COVID-19 at the emergency department (ED), general wards, and intensive care unit (ICU) were 17.9% (95% CI: 12.0–23.8%), 23.9% (95% CI: 15.2–32.7%), and 48.6% (95% CI: 41.0–56.1%), respectively. PE was more commonly located in peripheral than in main pulmonary arteries (pooled frequency of 65.3% [95% CI: 60.0–70.1%] vs. 32.9% [95% CI: 26.7–39.0%]; OR = 3.540 [95% CI: 2.308–5.431%]). Patients with PE had significantly higher D-dimer levels (pooled SMD of 1.096 [95% CI, 0.844–1.349]). D-dimer cutoff levels which have been used to identify patients with PE varied between 1000 and 4800 μg/L.

Conclusion The frequency of PE in patients with COVID-19 is highest in the ICU, followed by general wards and the ED. PE in COVID-19 is more commonly located in peripheral than in central pulmonary arteries, which suggests local thrombosis to play a major role. D-dimer assessment may help to select patients with COVID-19 for CTPA, using D-dimer cutoff levels of at least 1000 μg/L.

Key Points

- *The frequency of PE in patients with COVID-19 is highest in the ICU, followed by general wards and the ED.*
- *PE in COVID-19 is more commonly located in peripheral than in central pulmonary arteries.*
- *D-dimer levels are significantly higher in patients with COVID-19 who have PE.*

Keywords Coronavirus · Pulmonary embolism · Coagulation · Tomography · Diagnosis

Abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
CTPA	Computed tomography pulmonary angiography
ED	Emergency department
ICU	Intensive care unit
OR	Odds ratio
PE	Pulmonary embolism
SD	Standard deviation
SMD	Standardized mean difference

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic has caused dramatic effects on society. On March 21, 2021, more than 122 million people have been infected and more

than 2.7 million people have died of the disease worldwide [1]. Although approximately 80% of patients with COVID-19 have a favorable clinical course without hospitalization [2], approximately 20% of patients experiences severe respiratory disease [2]. A high incidence of thromboembolic events, including pulmonary embolism (PE), has been observed in COVID-19, which suggests that COVID-19 may induce intravascular coagulopathy [3–6]. PE may be a direct cause of death in patients with COVID-19, despite the use of antithrombotic prophylaxis [4, 6, 7]. Patients with COVID-19 who experience PE should be managed in a timely manner with therapeutic doses of anticoagulant therapy [8]. Computed tomography pulmonary angiography (CTPA) is the preferred imaging modality to detect PE [9]. To date, the frequency of PE in patients with COVID-19 is not completely clear. As such, it is still unclear which patients should undergo CTPA to detect PE. Unfortunately, clinical pretest probability scores, such as the Wells criteria [10], are unreliable to predict the occurrence of PE in patients with COVID-19 [11–14]. It has been suggested that assessment of D-dimer levels may help to improve risk stratification for PE [5, 15], but the exact value is also not completely clear. In order to overcome these gaps in knowledge, it was our purpose to investigate, in a meta-analysis, the frequency of PE in patients with COVID-19, and whether D-dimer assessment may be useful to select patients with COVID-19 for CTPA.

Materials and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [16]. Institutional review board approval was not applicable.

Study retrieval and selection

MEDLINE and Embase were searched using the following search string: (Corona OR Coronavirus OR Covid-19 OR SARS-Cov-2 OR 2019nCoV OR Wuhan-virus) AND (Computed tomography OR Computerized tomography OR Computed tomographic OR CT OR CAT OR CTPA) AND (pulmonary embolism OR PE OR pulmonary thromboembolism OR PTE OR pulmonary thrombosis). Furthermore, the journal *Radiology: Cardiothoracic Imaging* was manually searched for relevant studies (articles published by this journal were not listed yet in MEDLINE and Embase). The search was updated until March 14, 2021. Bibliographies of studies which were included in our meta-analysis were screened for potentially suitable references.

Original studies which reported the frequency of PE on CTPA scans performed in at least 10 patients with COVID-19 (regardless of PE frequency) were eligible for inclusion. Review articles, abstracts, and studies involving fewer than 10 patients were excluded. Using these selection criteria, titles and abstracts of studies were reviewed. The full text versions of potentially relevant studies were then reviewed to determine whether studies could be included in our meta-analysis. Bibliographies of included studies were screened for other potential relevant studies. Two reviewers (R.M.K. and H.J.A.A.) independently performed the study selection. Any discrepancies were solved by consensus with a third reviewer (T.C.K.).

Study data extraction and study quality assessment

Main study characteristics (country of origin, patient inclusion period, number of patients, age and gender of patients, indication for CTPA, use of antithrombotic prophylaxis before CTPA, and CT interpreter(s)) were extracted for each included study. The proportions of patients with and without PE were extracted. If reported, data were extracted for patients with COVID-19 who presented at the emergency department (ED), for patients with COVID-19 who had been admitted to general wards, and for patients with COVID-19 who had been admitted to the intensive care unit (ICU). Furthermore, we extracted the association between severity of COVID-19 at chest CT and PE, if reported by the included studies. We also extracted the locations of PEs (i.e., main, lobar, segmental, and subsegmental pulmonary arteries) on a per-patient basis if reported by the included studies. In addition, for studies which reported D-dimer levels for patients with and without PE, we extracted the mean values and standard deviations (SDs). Corresponding authors of studies which did not report mean values and SDs were contacted and requested to provide these values. We also extracted sensitivity and specificity values for different D-dimer cutoff levels, if reported by the included studies.

Study quality aspects were assessed by two independent reviewers (R.M.K. and H.J.A.A.) using items from the Newcastle-Ottawa quality assessment scale [17] which were adapted to our meta-analysis (Table 1). Any discrepancies were solved by consensus with a third reviewer (T.C.K.).

Statistical analyses

The frequencies of PE in patients with COVID-19 were determined for each included study and pooled with a random effects model. For studies which reported the frequency of PE in both patients with COVID-19 and those without COVID-19, differences were assessed by a chi-square test [18]. The frequencies of central (main and lobar) and peripheral (segmental and subsegmental) PEs were also pooled with a random effects model and the odds ratio (OR) of peripheral vs. central PEs was calculated. Differences in D-dimer levels

Table 1 Criteria to evaluate the quality of included studies

Quality items	Signaling questions
Type of cohort study	Does the study have a prospective or retrospective design?
Method of patient selection	Was a consecutive, randomly selected, or obviously representative series of patients included?
Patient spectrum	Were selection criteria for CTPA reported?
Blinded assessment of outcome	Were CTPA interpreters blinded to clinical information (i.e., study purpose or COVID-19 status of patients)?

between patients with COVID-19 vs. those without PE were assessed by calculating the standardized mean difference (SMD). The pooled SMD was estimated by a random effects model. Heterogeneity was tested by the I^2 statistic [19]. If significant heterogeneity was present (defined as $I^2 > 40\%$ [20]), subgroup analyses were performed to explore potential sources of heterogeneity. Predefined covariates were "indication for CTPA" (study reported that was CTPA only performed if PE was clinically suspected vs. study reported that CTPA was performed for triaging or on a routine basis, but not necessarily because of clinically suspected PE), "use of antithrombotic prophylaxis before CTPA" (100% vs. < 100% of included patients who used antithrombotic prophylaxis before CTPA), and "way of CTPA interpretation" (blinding vs. no blinding of CTPA interpreters to clinical information). Statistical analyses were performed using the Open Meta-Analyst software package [21], and MedCalc Statistical Software (MedCalc Software) [22]. p values < 0.05 were considered statistically significant for all analyses.

Results

Study retrieval and selection

The study selection process is summarized in Fig. 1. After screening titles and abstracts, 130 potentially relevant studies remained and were retrieved in full text. After reviewing the full text, 52 studies were excluded because there was no reporting of PE frequency data with respect to the number of CTPA scans performed in patients with COVID-19, 6 studies were excluded because these studies did not allow separate data extraction of patients with and without COVID-19, 2 studies were excluded because they comprised fewer than 10 patients with COVID-19, and 1 study was excluded because in this study PE was also determined based on clinical grounds rather than by CTPA only. Two additional references were found by screening bibliographies of remaining studies. Finally, 71 studies [11, 23–92], which comprised a total of 8086 patients with COVID-19 who underwent CTPA to evaluate for PE (median of 55 patients per study, range 10–1240), were included in our meta-analysis. Main study characteristics are displayed in Table 2.

Study quality

Details with regard to individual study quality are displayed in Supplemental Table 1. Eight studies (11.3%) had a prospective design, whereas 58 included studies (81.7%) had a retrospective design, whereas in 5 studies (7.0%) it was not reported whether the study design was prospective or retrospective. All but one of the included studies consecutively or randomly selected patients, or obviously comprised a representative series of patients. In 55 studies (77.5%), patient selection criteria for CTPA were reported, in 15 studies (21.1%), patient selection criteria for CTPA were not reported, whereas in 1 study (1.4%), patient selection criteria for CTPA were only reported for a subset of patients. CTPA interpreters were blinded to clinical information in 15 studies (21.1%), and unblinded in 2 studies (2.8%) whereas this was not clear (not reported) in the remaining 54 studies (76.1%).

Frequency of PE in patients with COVID-19

Pooled frequency of PE in all included patients with COVID-19 was 32.1% (95% confidence interval [CI]: 28.5–35.9%). Pooled frequency of PE was lowest in patients who presented at the ED (17.9% [95% CI: 12.0–23.8%]) (Fig. 2), followed by patients who had been admitted to general wards (23.9% [95% CI: 15.2–32.7%] (Fig. 3). In patients with COVID-19 who had been admitted to the ICU, pooled frequency of PE was highest (48.6% [95% CI: 41.0–56.1%]) (Fig. 4).

Significant heterogeneity was present across the included studies ($I^2 \geq 80\%$). No potential sources of heterogeneity were identified ($I^2 > 85\%$) for subgroups according to "indication for CTPA," "use of antithrombotic prophylaxis before CTPA," and "way of CTPA interpretation." In two studies which routinely performed CTPA at the ED (regardless of clinical suspicion of PE), PE frequencies in COVID-19 patients were 2.1% (1/48) and 5.7% (4/70), respectively [29, 50]. In two other studies which routinely performed CTPA at the ICU (regardless of clinical suspicion of PE), PE frequencies in COVID-19 patients were 47.2 % (34/72) and 60.0% (12/20),

Table 2 Main characteristics of the included studies

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
Alharthy et al [23]	Saudi Arabia	May	-25 -NR -NR	Resistant hypoxemia	All patients (100%)	NR
Alonso-Fernández et al [24]	Spain	April 6–April 17	-30 -Median 64.5 years (IQR 55.8–71.3) -19 males	Suspected PE	26 patients (86.7%)	An expert radiologist
Artifoni et al [25]	France	March 25–April 10	-34 -NR -NR	Suspected PE	All patients (100%)	NR
Baccellieri et al [26]	Italy	April 2–April 18	-87 -NR -NR	NR	All patients (100%)	NR
Bellmunt-Montoya et al [27]	Spain	April 2020	-38 -NR -NR	Sudden respiratory or cardiovascular deterioration and signs of pulmonary hypertension, right ventricular dilatation or dysfunction on transthoracic echocardiography	NR	NR
Benito et al [28]	Spain	March 9–April 15	-76 -Median 60–66 years -51 males	Patients whose partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2:FiO_2) ratio worsened or failed to improve, associated with an increasing or persistently high D-dimer level (> 3,000 ng/mL) and/or hemodynamic deterioration or other "classic" symptoms of PE, such as pleuritic chest pain, hemoptysis, syncope, and/or signs of right ventricular strain.	All patients (100%)	NR
Birk et al [29]	UK	March 25–April 30	-48 -NR -NR	All patients underwent CTPA for COVID-19 triage	No patients (0%)	Consultant radiologists specialized in body imaging
Bompard et al [30]	France	March 1–April 16	-135 -Median 64 years (IQR 54–76) -94 males	In case of doubt between COVID-19 pneumonia and PE, after clinical probability assessment and D-dimer assessment	All patients 100%)	Two experienced radiologists
Brüggemann et al [31]	The Netherlands	April 6–May 3	-60 -Mean 68 years (± 11.7) -42 males	Respiratory deterioration or clinical suspicion of PE	23 patients (38.3%)	Attending chest radiologist
Cavagna et al [32]	Italy	March 20–May 3	-101			

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
			-Mean 64.1 years (± 15.0) -82 males	Sudden onset of clinical deterioration with unexplained worsening of dyspnea, symptoms suggestive for PE, D-dimer elevation, or in case of mismatch between clinical worsening and chest radiograph stability	All patients (100%)	Two radiologists with > 5 years, and > 20 years of experience in chest imaging, in consensus
Cerda et al [33]	Spain	March 1–April 24	-92 -Mean 68.1 years (± 13.2) -68 males	New or worsening dyspnea or oxygen desaturation, syncope or hemodynamic instability, or chest pain	All patients (100%)	Two expert thoracic radiologists
Chen J et al [34]	China	January–February	-25 -Median 65 years (range 36–78) -15 males	Elevated D-dimer level or accompanying symptom(s), including chest pain, hemoptysis, and dyspnea	NR	Two radiologists experienced in thoracic radiology with 20 and 22 years of experience
Contou et al [35]	France	March 13–April 24	-26 -Mean 63 years -22 males	Sudden circulatory (introduction or significant increase of the dose of vasopressor) or/and respiratory (significant increase of FiO_2 requirement) worsening with no obvious explanation such as ventilatory associated pneumonia or other source of sepsis	NR	NR
Darwish et al [36]	Saudi Arabia	May 1–July 14	-25 -Mean 49 years (± 11) -NR	Suspected PE	NR	NR
De Cobelli et al [37]	Italy	March 29–April 9	-55 -Median 62 years (IQR 56–71) -39 males	Suspected PE	NR	Two radiologists experienced in thoracic imaging, with 28 and five years of experience
Espallargas et al [38]	Spain	March 18–April 11	-47 -Median 65 years (range 30–94) -30 males	Suspected PE	36 patients (76.6%)	Radiologists with 12 and 29 years of experience
Fang et al [39]	UK	March 23–April 19	-93 -Median 57 and 62 years -60 males	NR	NR	Two radiologists with 4 years of experience in cancer imaging and with 6 years of experience in thoracic imaging

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
Fauvel et al [40]	France	February 26–April 20	-1240 -Mean 64 years (± 17) -721 males	If supplementary oxygen was needed in COVID-19 patients with limited disease extension, or when unenhanced CT findings could not explain the severity of respiratory failure.	837 patients (67.5%)	A senior radiologist
Freund et al [41]	France, Spain, Belgium, Italy, Chile, and Canada	February 1–April 10	-974 -NR -NR	Suspected PE	NR	NR
García-Ortega et al [42]	Spain	March 8–April 25	-73 -Mean 65.4 years (± 16) -52 males	Age ≥ 18 years and elevated D-dimer levels	68 patients (93.2%)	Two independent experienced thoracic radiologists
Gervaise et al [43]	France	March 14–April 6	-72 -Mean 62.3 years (range 22–92) -54 males	Mainly based on a worsening of the patient's clinical condition with new onset of dyspnea, desaturation, or chest pain and also an increase in D-dimer levels	NR	Two radiologists with 10 and 12 years of experience in thoracic imaging
Grillet et al [44]	France	March 15–April 14	-100 -Mean 66 years (± 13) -70 males	Patients with severe clinical features of COVID-19 infection	NR	Two chest radiologists with 11 and 6 years of experience
Grillet et al [45]	France	March 16–April 22	-85 -Mean 65 years (± 13) -55 males	Clinical signs of severe grade infection were present (oxygen saturation below 92%, polypnea over 25 cycles per minute, fever > 40 °C, increasing oxygen needs), need for invasive mechanical ventilation, or when the patient suffered from comorbidities of active neoplasia, immunosuppression, history of organ or bone-marrow transplantation.	NR	Two chest radiologists with 11 and 2 years of experience in chest imaging
Hamadé et al [46]	France	March 25–April 8	-12 -NR -NR	Suspected PE	NR	NR
Hammer et al [47]	USA	March 1–May 1	-17 -NR -NR	NR	All patients (100%)	NR
Helms et al [48]	France	March 3–March 31	-99 -NR -NR	Based on clinical parameters (worse PaO_2/FiO_2 despite inhaled nitric oxide or after prone positioning or hemodynamic impairment requiring fluid challenge and/or increased	All patients (100%)	Consultant radiologists specialized in emergency radiology

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
				norepinephrine infusion rate, dilated right ventricle-even without acute cor pulmonale) or evolution of laboratory parameters (a rapid elevation of D-dimer levels despite anticoagulation)		
Ippolito et al [49]	Italy	March 5–April 24	-170 -Mean 63 years (± 12) -116 males	Chest pain, worsening of respiratory symptoms, irregular or new-onset rapid heartbeat, worsening of fever, aggravation of arterial blood gas parameters, and a marked increase over time of D-dimer and/or fibrinogen values	NR	A radiologist with 15 years of experience in chest imaging and a resident radiologist with 4 years of experience, in consensus
Jalaber et al [50]	France	March 26–April 17	-70 -Mean 65 years (range 21–97) -44 males	All patients suspected of COVID-19	NR	Experienced chest radiologist
Jevnikar et al [51]	France	April 15–May 23	-106 -Median 63 years (range 53–82) -48 males	All adult patients with a diagnosis of COVID-19 at the time of hospital admission	NR	A senior radiologist and a pulmonologist
Kaminetzky et al [52]	USA	March 13–April 5	-62 -Mean 57.8 years (range 28–89) -40 males	Hypoxia in 17, respiratory distress in 16, elevated D-dimer in 14, tachycardia in 7, chest pain in 4, extremity swelling in 1, and 3 had an indication not specified above	25 patients (40.3%)	Two board-certified thoracic radiologists with 16 and 22 years of experience in thoracic imaging
Khan et al [53]	UK	April 20–May 13	-13 -NR -NR	NR	> 10 patients (> 76.9%)	NR
Kirsch et al [54]	USA	February 1–July 15	-64 -Mean 55 years (± 16) -35 males	NR	NR	NR
Lang et al [55]	USA	March 23–April 6	-48 -Mean 58 years (± 19) -25 males	NR	NR	Two thoracic radiologists with 11 years and 2 years of thoracic imaging subspecialty experience
Larsen et al [56]	France	March 11–April 20	-35 -Median 66 years (IQR 56–78)	Hypoxemic pneumonia (pneumonia requiring oxygen supplementation to achieve oxyhemoglobin saturation > 94%)	28 patients (80%)	Two radiologists and at least two pulmonologists

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
Lee et al [57]	USA	March 20–May 3	-27 males -86 -NR-NR	NR	NR	NR
Lodigiani et al [59]	Italy	February 13–April 10	-30 -NR -NR	NR	NR	NR
Loffi et al [60]	Italy	February 22–May 15	-333 -Median 67 years (IQR 57–77) -211 males	Inadequate clinical response to high oxygen flow therapy, elevated D-dimer levels, or signs of right ventricle dysfunction at echocardiography	223 patients (67%)	One senior radiologist
Léonard-Lorant et al [58]	France	March 1–March 31	-106 -Median 64 years -70 males	Suspicion of PE in 67 and other indication in 39	NR	A single reader
Mak et al [61]	UK	March–May	-51 -Mean 45 years (range 26–66) -38 males	All patients receiving ECMO	NR	Two cardiothoracic radiologists in consensus (7 and 9 years of experience)
Martini et al [63]	Switzerland	February–April	-38 -Median 59 years (range 32–89) -18 males	Clinical signs and symptoms of deep vein thrombosis, tachypnea, decreased oxygen saturation, or high oxygen demand	8 patients (21.1%)	Two radiologists
Martínez Chamorro et al [62]	Spain	March 15–April 30	-342 -Mean 62.4 years (± 16.8) -58 males	Clinical deterioration with the appearance or worsening of dyspnea, desaturation, chest pain, and elevated D-dimer.	NR	A third or fourth year radiology resident, supervised by at least one radiologist from the emergency department or from the chest section, with at least 15 years of experience. Discrepancies were resolved by consensus between two of the more experienced radiologists.
Meiler et al [64]	Germany	March 1–April 20	-50 -Mean 60.4 years (± 10.1) -34 males	NR	NR	Two junior radiologists with subspeciality training in thoracic radiology, and A senior thoracic radiologist (for equivocal cases)
Mestre-Gómez et al [65]	Spain	March 30–April 12	-91 -Median 65 years	Respiratory deterioration not attributable to other causes, data on acute respiratory distress without improvement despite specific treatment	23 of 29 patients with PE (≥ 25.3%)	NR

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
			-62 males	or elevation of D-dimer levels in discordance with other inflammatory parameters		
Minuz et al [66]	Italy	March 30–April 6	-10 -NR -NR	Persistent respiratory impairment and a D-dimer value at least five times the upper reference limit.	NR	NR
Mirsadraee et al [68]	UK	March 19–June 23	-72 -Mean 52 years (± 10) -53 males	Routine in all patients who are admitted to ICU	12 patients (16.7%)	Two consultant cardiothoracic radiologists, with disagreements resolved by consensus.
Miró et al [67]	Spain and France	March 6–April 15	-320 -NR -NR	PE suspected based on patient signs and symptoms	NR	NR
Moll et al [69]	USA	March 7–April 13	-25 -NR -NR	NR	NR	NR
Monfardini et al [70]	Italy	March 1–March 31	-34 -NR -NR	Sudden oxygen desaturation coupled with a moderate to high risk of PE according to the Wells score and D-dimer levels	8 patients (23.5%)	Two experienced thoracic radiologist with 15 and 20 years of experience
Mouhat et al [71]	France	March 15–April 16	-162 -Mean 65.57 years (± 13.00) -109 males	Oxygen saturation measured by pulse oximetry ≤ 93% in room air, breathing rate of ≥ 30 breaths/minute or rapid clinical worsening	141 patients (87.0%)	Two chest radiologists
Mueller-Peltzer et al [72]	Germany	March 8–April 15	-16 -Mean 62.2 years (range 47–77) -10 males	When likelihood of PE was considered high	4 patients (25%)	Two radiologists with 6 and 13 years of experience in thoracic radiology
O'Shea et al [73]	USA	March 17–April 6	-94 -NR -NR	NR	NR	Radiologist with 7 years of experience in cardiovascular imaging
Ooi et al [74]	UK	March 1–April 30	-84 -Mean 59.8 years, SD 16.59 -42 males	High D-dimer level (36), shortness of breath (29), hypoxia or increasing oxygen requirement (27), chest pain, discomfort or tightness (25), hemoptysis (7), tachycardia (6), hypotension (5), abnormal ECG changes (5), fever (4), following beside echocardiogram (3), high Wells score (3), intubated and ventilated (5), not improving on	NR	NR

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
				extracorporeal membrane oxygenation (ECMO) (3), recent travel (2)		
Parzy et al [75]	France	March 18–May 5	-13 -Median 50 years (IQR 43–62) -9 males	Routinely after veno-venous ECMO retrieval	All patients (100%)	NR
Patel et al [76]	UK	March 17–April 10	-39 -Median 52.5 years (range 29–79) -32 males	NR	All patients (100%)	Two thoracic radiologists of 14 and 24 years of experience
Planquette et al [78]	France	March 1–April 20	-269 -Media 63 years (IQR 53–79) -33 males	Suspected PE	NR	NR
Poissy et al [79]	France	February 27–March 31	-34 -Median 57 years (range 29–80) -13 males	Suspected PE	20 of 22 patients with PE (≥ 58.8%)	NR
Poyiadji et al [80]	USA	March 16–April 18	-328 -Mean 61.3 years -140 males	NR	122 of 328 patients (37.1%)	Thoracic, abdominal, or emergency radiologists, all with 2-40 years of experience
Pérez Dueñas et al [77]	Spain	March 23–April 8	-81 -Mean 64 years -64 males	Clinical suspicion of PE due to presence of sudden dyspnea, chest pain, hemoptysis, respiratory failure severe not corrected with high O_2 flow, and/or D-dimer level > 500 ng/mL	NR	Two expert radiologists in thromboembolic lung disease with > 15 years of experience
Rali et al [81]	USA	April 1–April 27	-49 -NR -NR	High index of clinical suspicion	All patients (100%)	NR
Ramadan et al [82]	USA	March 1–June 1	-367 -Mean 59.7 years -145 males	NR	NR	NR
Schiaffino et al [83]	Italy	March 1–April 30	-45	Presence of lower-limb deep vein thrombosis at ultrasound Doppler examination, onset or	All patients (100%)	A radiologist with 15 years of experience in body and chest

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
			-Median 67 years (IQR 60–76) 34 males	worsening of dyspnea, and worsening or less-than-expected improvement of the PaO_2/FiO_2 ratio.		CT
Scialpi et al [84]	Italy	March–May	-10 -NR -NR	Clinical and laboratory data which were suspicious for PE	NR	Two radiologists with at least 25 years of experience in chest CT
Shahin et al [85]	UK	NR	-10 -Mean 70 years (± 16) -6 males	Suspected acute PE based on clinical assessment and elevated D-dimer	NR	NR
Taccone et al [86]	Belgium	March 10–April 20	-40 -Mean 61 years (range 57–66) -28 males	NR	22 patients (55.0%)	One radiologist
Thomas et al [87]	UK	March 15–NR	-11 -NR -NR	Clinical suspicion (e.g., unexplained hypotension or hypoxia felt disproportionate to the pneumonia)	All patients (100%)	NR
Tung-Chen et al [88]	Spain	March–April	-51 -Mean 61.4 years (± 17.7) -28 males	Suspected PE	NR	Two radiologist trainees with 2-4 years of experience, under the supervision of a senior radiologist with more than 10 y of experience
Ventura-Díaz et al [89]	Spain	March 1–April 30	-242 -Median 68 years (IQR 55–78) -151 males	Suspected PE	NR	NR
Vlachou et al [90]	UK	March 23–April 5	-39 -Mean 62.3 years (± 15) -52 males	Increasing oxygen requirements or refractory hypoxia, not improving on oxygen, elevated D-dimer, or tachycardia	NR	NR
Whyte et al [11]	UK	March 3–May 7	-214 -Mean 61.1 years -129 males	Patients with suspected PE undergo a two-level PE Wells score. Imaging is not undertaken for those considered "PE unlikely" by the Wells rule (score < 4) in conjunction with a D-dimer level < 500 ng/mL	206 patients (96.3%)	NR
Zhang et al [91]	UK	March 3–May 2	-43	All patients admitted for veno-venous ECMO		NR

Table 2 (continued)

Study	Country	Inclusion period (2020)	-Number of patients with COVID-19 who underwent CTPA -Age -Gender	Selection criteria for CTPA	Antithrombotic prophylaxis before CTPA (% of all included patients)	CTPA interpreter(s)
			-Median 46 years (IQR 35.5–52.5) -33 males		All patients without hemorrhagic complications (≈ 100%)	
Zotzmann et al [92]	Germany	March 8–May 31	-20 -Mean 61.6 years (± 9.9) -14 males	All patients with ARDS and SARS-CoV2 infection	5 patients (25%)	NR

IQR interquartile range, *NR* not reported

respectively studies [68, 92]. Six studies reported a significant association between severity of COVID-19 at chest CT and PE, whereas 13 studies did not find a significant association (Supplemental Table 2).

PE location

PE was more commonly located in peripheral than in main pulmonary arteries (pooled frequency of 65.3% [95% CI: 60.0–70.1%] vs. 32.9% [95% CI: 26.7–39.0%]; OR = 3.540 [95% CI: 2.308–5.431%]).

PE in patients with COVID-19 and association with D-dimer levels

Patients with COVID-19 and PE had significantly higher D-dimer levels than patients with COVID-19 and no PE (pooled SMD of 1.096 [95% CI, 0.844–1.349]; I^2 = 89%) (Fig. 5). Sensitivity and specificity values for different D-dimer cutoff levels are displayed in Table 3. D-dimer cutoff levels which have been used to identify patients with PE varied between 1000 and 4800 μg/L. All studies listed in Table 3 used the conventional D-dimer score. Only one study also used age-adjusted D-dimer cutoffs [93], yielding a sensitivity of 94% and a specificity of 35% [33].

Discussion

This meta-analysis showed that the frequency of PE in COVID-19 was highest in patients who were in the ICU (pooled frequency of 48.6%), followed by patients who were in general wards (pooled frequency of 23.9%), and by patients who presented at the ED (pooled frequency of 17.9%). PE was more commonly located in peripheral than in main pulmonary arteries (pooled frequency of 65.3% vs. 32.9%). Patients with PE had significantly higher D-dimer levels than patients without PE.

Fifty-eight of the 71 included studies (81.7%) had a retrospective design. However, there was no evidence of selection bias, as all but one of the studies included a consecutive, randomly selected, or obviously representative series of patients. Selection criteria for CTPA were reported in the majority of included studies (77.5%), which benefits the generalizability of study results. In only 21.1% of included studies, it was reported that CTPA interpreters were blinded to clinical information. Non-blinding could have biased the results to either overcalling or undercalling PE frequency on CTPA.

The findings of our meta-analysis suggest that the frequency of PE in patients with COVID-19 increases with increasing disease severity (ICU > general wards and ED). This is supported by six studies which reported a significant association between severity of lung parenchymal abnormalities at CT

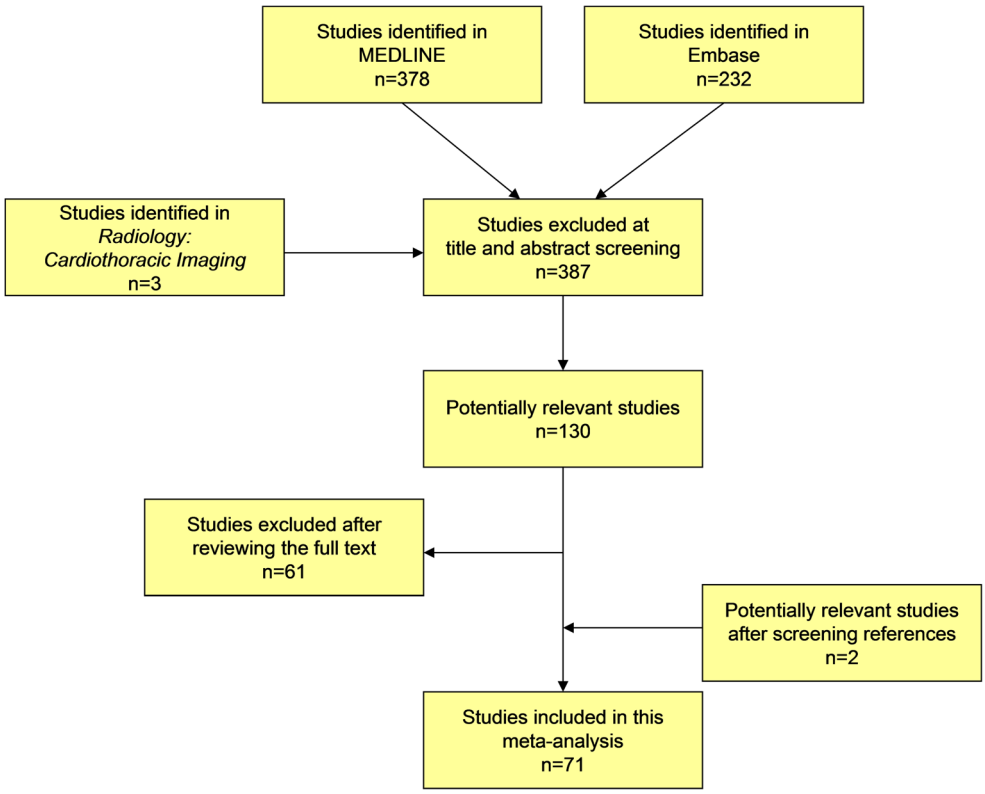

Fig. 1 Flow diagram of the study selection process

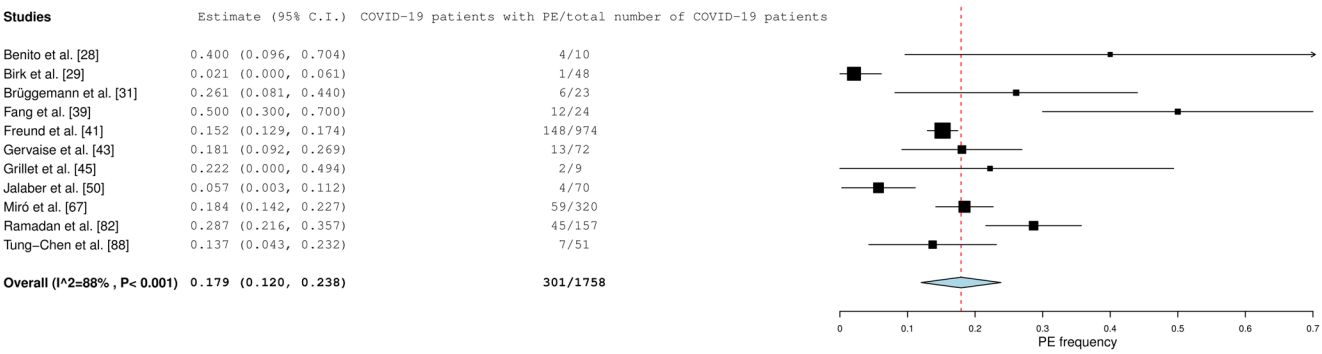

Fig. 2 Frequency of PE in patients with COVID-19 who presented at the ED

and PE [32, 40, 44, 45, 71, 74]. However, such an association was not demonstrated in 13 other studies [24, 30, 31, 37, 42, 43, 49, 50, 52, 60, 62, 78]. Therefore, there are probably other COVID-19- and host-related factors that are associated with the occurrence of PE. Further studies are required to improve our understanding of the pathophysiology of PE in COVID-

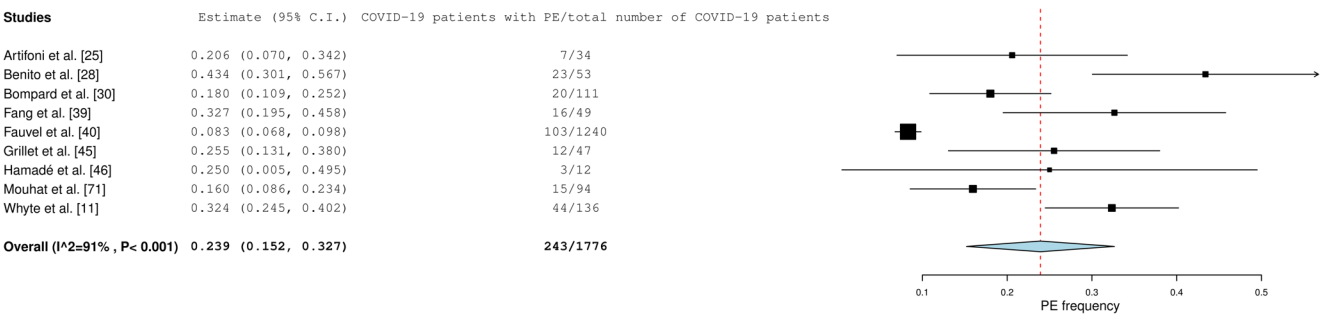

Fig. 3 Frequency of PE in patients with COVID-19 who had been admitted to general wards

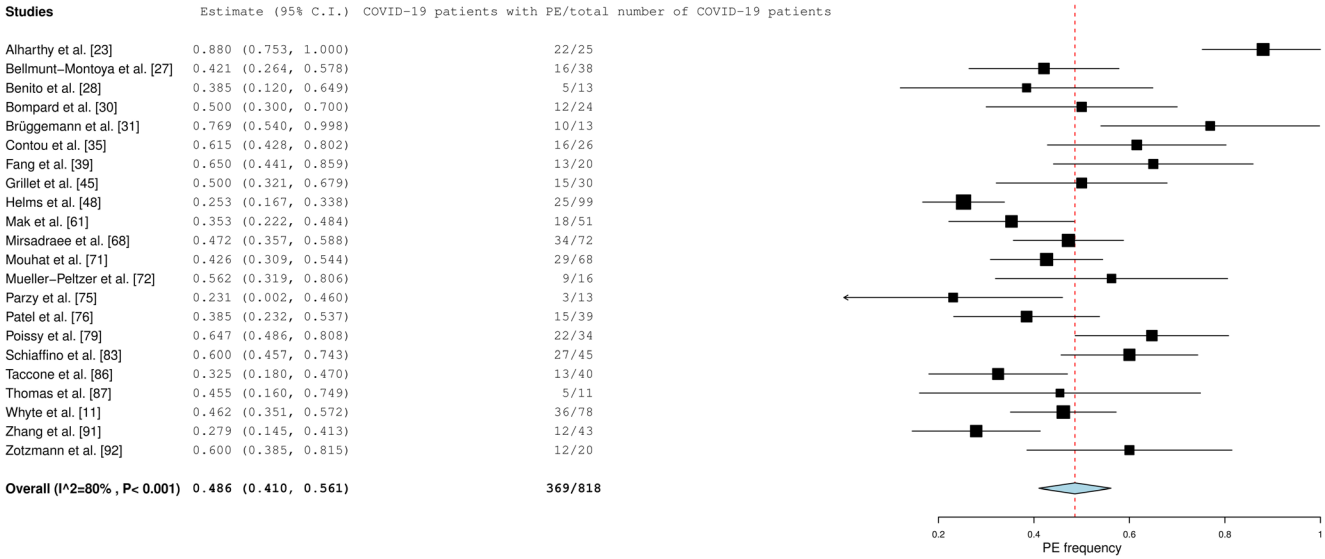

Fig. 4 Frequency of PE in patients with COVID-19 who had been admitted to the ICU

19. Furthermore, the observed frequency of PE depends on the selection criteria for CTPA. In the far majority of included studies, it was reported that CTPA was performed because of clinically suspected PE. In only two studies, CTPA was routinely performed at the ED (regardless of clinical signs of possible PE), with relatively low yields of only 2.1% and 5.7% [29, 50]. In two other studies which routinely performed CTPA in COVID-19 patients at the ICU (regardless of clinical signs of possible PE), PE frequencies were high: 47.2% and 60.0%, respectively [68, 92]. These findings in unselected samples of patients confirm that frequency of PE is higher in ICU patients compared to patients who present at the ED.

Our findings contrast those in patients from the general population without COVID-19, where PE has been reported to occur in main pulmonary arteries as frequent as or more frequently than in peripheral arteries [94–96]. Therefore, the underlying pathomechanisms may be different. The relatively high frequency of peripheral PE suggest that local thrombosis may play a more important role in the development of PE (or pulmonary artery thrombosis) in COVID-19 [37, 55, 97, 98]

Table 3 Sensitivity and specificity values for different D-dimer cutoff levels to diagnose PE

Study	D-dimer cutoff level	Sensitivity	Specificity
Alonso-Fernandez et al [24]	2500 μg/L	80%	51%
Cerda et al [33]	2036 μg/L	75%^	69%^
	Age-adjusted cutoff levels	94%^	35%^
Kaminetzky et al [52]	1394 μg/L	95%	71%
Léonard-Lorant et al [58]	2660 μg/L	100%	67%
Loffi et al [60]	2370 μg/L	70%	62%
Mouhat et al [71]	2590 μg/L	83%	84%
Ooi et al [74]	2247 μg/L	72%	74%
Planquette et al [78]	1500 μg/L	76%	65%
Ramadan et al [82]	2000 μg/L	78%*	67%*
	1000 μg/L	63%#	66%#
		94%*	30%*
		89%#	23%#
Taccone et al [86]	3647 μg/L	75%	92%
Ventura-Diaz et al [89]	2903 μg/L	81%	59%
Whyte et al [11]	4800 μg/L	75%	78%

*ED patients

Inpatients

^3 weeks after COVID-19 symptom onset

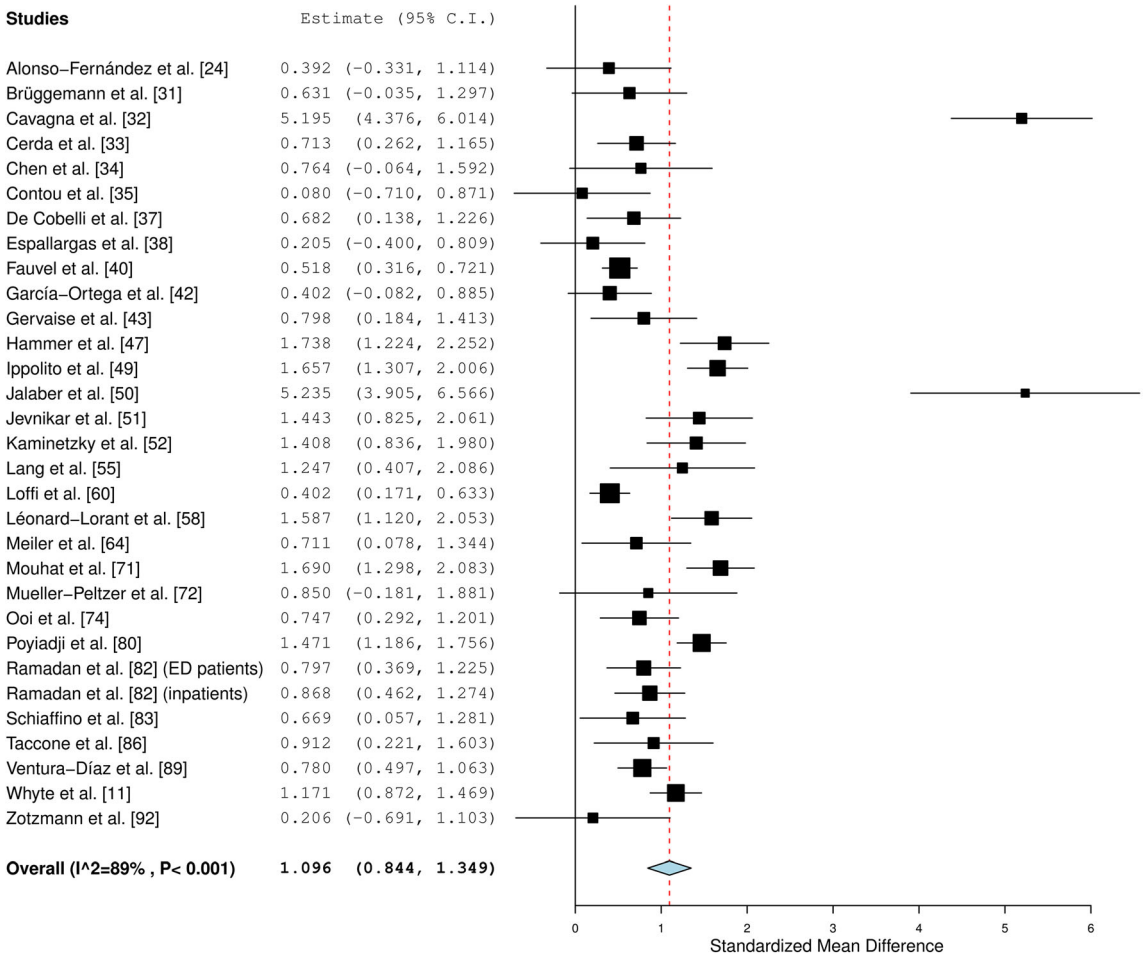

Fig. 5 Association between D-dimer levels and PE in patients with COVID-19

rather than the classic thromboembolism originating from the leg or pelvic veins in patients without COVID-19 [99]. This hypothesis is supported by in vivo chest CT studies, where vascular thickening, a potential sign of vascular inflammation, endothelial damage, and microthrombosis [55], is observed in most symptomatic patients with COVID-19 [100]. Pathological studies in patients with COVID-19 also confirm the local immunothrombosis hypothesis [97, 98]. Accordingly, the term MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) has been coined as a new name for severe pulmonary COVID-19, in which alveolar viral damage is followed by an inflammatory reaction and by microthrombosis [97, 101–103]. It may become obsolete to call this pathophysiological disorder PE.

Subgroup analysis did not indicate that the use of antithrombotic prophylaxis was associated with a lower frequency of PE in patients with COVID-19. This implies that physicians should remain alert for the occurrence of PE even in patients who receive antithrombotic prophylaxis. D-dimer levels were found to be significantly higher in patients with PE (pooled SMD of 1.096), which indicates that a rise in D-dimer levels is not only a marker of pneumonia severity but is also associated with a higher risk of PE. Therefore, D-dimer assessment may help to decide which patients with COVID-19 should undergo CTPA to detect PE. However, there is no uniformly accepted D-dimer threshold to discriminate COVID-19 patients with and without PE. Twelve studies used different D-dimer cutoff levels (varying between 1000 and 4800 μg/L), yielding sensitivity and specificity values which varied between 63–100% and 23–84%, respectively [11, 24, 33, 52, 58, 60, 71, 74, 78, 82, 86, 89]. These D-dimer cutoff levels were at least twice as high compared to the conventional D-dimer cutoff level of 500 μg/L, which is usually employed in the general population as a screening test for venous thromboembolism [104, 105]. In non-COVID-19 patients aged 50 or more, the application of age-adjusted D-dimer cutoffs has shown to increase specificity without modifying sensitivity [106]. Only one of the studies included in our meta-analysis also used age-adjusted D-dimer cutoffs, yielding high sensitivity (94%) but poor specificity (35%) [33]. More research is needed to investigate whether the use of age-adjusted D-dimer cutoffs can

improve the clinical utility of D-dimer testing in patients with COVID-19.

Our study has some limitations. First, in the far majority of included studies, CTPA was only performed in case of clinically suspected PE. Therefore, the true prevalence of PE in patients with COVID-19 remains to be elucidated. Second, due to incomplete and unstandardized reporting, we could not adjust the frequency of PE for well-known risk factors for PE (such as cancer, history of previous venous thromboembolism, duration of hospitalization, obesity, and cardiovascular disease [107]) and type and dosage of antithrombotic prophylaxis. Third, there was a great deal of heterogeneity in the patient population and the indication for CTPA in each included study. Although we attempted to group the studies into ED, general wards, and ICU patients, this delineation may be problematic due to the unpredictable course of COVID-19 and the fact that a patient discharged from the ED could become an ICU ARDS patient within a matter of a week. Furthermore, statistical heterogeneity still remained in each of these groups. Fourth, PE was determined by CTPA, which has a good but not perfect sensitivity in PE detection [9]. Although they may be clinically less relevant [108], smaller subsegmental PEs may have been missed by CTPA. This could have resulted in an underestimation of PE frequency.

In conclusion, the frequency of PE in patients with COVID-19 is highest in the ICU, followed by general wards and the ED. PE in COVID-19 is more commonly located in peripheral than in central pulmonary arteries, which suggests local thrombosis to play a major role. D-dimer assessment may help to select patients with COVID-19 for CTPA, using D-dimer cutoff levels of at least 1000 μg/L.

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Informed consent Written informed consent was not required for this study because of the meta-analysis.

Ethical approval Institutional Review Board approval was not required because of the meta-analysis.

Methodology
• Multicentre study

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