Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Risk factors for pulmonary embolism in patients with COVID-19: a systemic review and meta-analysis

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ABSTRACT

Purpose: To detect the risk factors for pulmonary embolism (PE) in patients with COVID-19.
Methods: Studies were searched for in PubMed, Cochrane Library, Web of Science, and EMBASE. Two authors independently screened articles and extracted data. The data were pooled by meta-analysis and three subgroup analyses were performed.
Results: Of the 2210 articles identified, 27 studies were included. Pooled analysis suggested that males (odds ratio (OR) 1.49, 95% confidence interval (CI) 1.26–1.75, $P = 0.000$), obesity (OR 1.37, 95% CI 1.03–1.82, $P = 0.033$), mechanical ventilation (OR 3.34, 95% CI 1.90–5.86, $P = 0.000$), severe parenchymal abnormalities (OR 1.92, 95% CI 1.43–2.58, $P = 0.000$), ICU admission (OR 2.44, 95% CI 1.48–4.03, $P = 0.000$), and elevated D-dimer and white blood cell values (at two time points: hospital admission or closest to computed tomography pulmonary angiography) ($P = 0.000$) correlated with a risk for PE occurrence in COVID-19 patients. However, age and common comorbidities had no association with PE occurrence. Computed tomography pulmonary angiography, unclear-ratio/low-ratio, and hospitalization subgroups had consistent risk factors with all studies; however, other subgroups had fewer risk factors for PE.
Conclusions: Risk factors for PE in COVID-19 were different from the classic risk factors for PE and are likely to differ in diverse study populations.

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has rapidly spread worldwide and caused more than 1 billion infections and 2 million deaths to date (Ackermann et al., 2020). The pathophysiology of COVID-19 has not yet been fully revealed. However, the direct viral toxicity (Alonso-Fernández et al., 2020), endothelial cell damage, and dysregulation of the immune response (Ameri et al., 2020) are widely believed to participate in the process (Artifoni et al., 2020). Emerging evidence has revealed that pulmonary embolism (PE) is a common complication in patients with COVID-19, with a higher incidence rate of 5–19% (Bavaro et al., 2020, Benito et al., 2020, Bilaloglu et al., 2020) and mortality rate of 8.7–45.1% (Bompard et al., 2020, BujaL et al., 2020, Bunce et al., 2011) than that in patients without COVID-19 (Ceriani et al., 2010, Chen et al., 2020) (incidence: 1.7–7.5%, mortality: 6.8%). Importantly, PE in patients with COVID-19 has been found to be different from classic PE in patients without COVID-19 in demographic, clinical, and laboratory characteristics (Chi et al., 2020, Choi et al., 2020). Even the traditional etiology of PE – venous thrombi dislodging and traveling as emboli to the pulmonary arteries (Connors and Levy, 2020) – has been suspected in COVID-19 patients (Contou et al., 2020, Egger et al., 2011, Fang et al., 2020). Some researchers have proposed a new hypothesis of pulmonary microvascular thrombosis, according to the unusual autopsy finding in COVID-19 that thrombosis and microangiopathy are common in the small vessels and capillaries of the

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lungs (Contou et al., 2020, Egger et al., 2011, Fang et al., 2020). Therefore, the risk factors for PE in patients with COVID-19 may differ from the classic ones and this is supported by several studies (Bompard et al., 2020, Fauvel et al., 2020, Flumignan et al., 2020, Fox et al., 2020). However, the results on this issue have been inconsistent. One systemic review without sub-analysis of PE recently stated the risk factors of venous thrombus embolism (VTE) in COVID-19, and they were different from the classic ones (Gervaise et al., 2020). Considering that PE in COVID-19 may not only originate from deep vein thrombosis, the detection of risk factors for PE is necessary.

At present, as clinical judgment lacks standardization (such as Wells, the revised Geneva prediction rule, or risk factors), the screening of suspected PE for computed tomography pulmonary angiography (CTPA) in patients with COVID-19 is mostly based on the empirical evaluation of clinicians. The common reasons are unexplained: respiratory deterioration, a rapid increase in D-dimer, or clinical symptoms of PE (Bompard et al., 2020, Choi et al., 2020, Flumignan et al., 2020, Fox et al., 2020). These make a low PE judgment rate with high heterogeneity between studies in COVID-19 (positive CTPA: 8–44%) (Bompard et al., 2020, Fauvel et al., 2020, Grillet et al., 2020) compared with the classic PE judgment using Wells or the revised Geneva prediction rule (confirmed PE expected to be 0–10% in the low-probability category and 65% in the high-probability category) (Ceriani et al., 2010, Gupta and Madhavan, 2020). Also, this rate may be overestimated because of the cautious screening strategy of suspected PE adopted to reduce cross-infection (Hajra et al., 2020, Jalaber et al., 2020). Therefore, it is essential to assess the risk factors for PE in COVID-19 and, aside from improving PE detection, risk factors can also promote the prevention and management of PE.

Therefore, this meta-analysis was conducted to detect the risk factors for PE in patients with COVID-19, along with subgroup analyses, considering the clinical practicability. It is believed that this is the first systematic review to do this and it is hoped that it can help physicians in diagnosing and managing PE. At the same time, it can promote an awareness of the clinical prediction rules for PE in patients with COVID-19, which is similar to the Geneva or Wells score.

Methods

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and registered with PROSPERO (CRD42020207652).

Citation search and selection

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched from 01 January 2019 to 28 December 2020, with no publication language limited. The following search strategy was used: ("pulmonary embolism" OR "lung embolism" OR "pulmonary thromboembolism" OR "lung thromboembolism") AND ("COVID-19" OR "coronavirus disease 2019" OR "2019-nCoV Disease" OR "2019-nCoV Infection" OR "SARS-CoV-2 Disease" OR "SARS-CoV-2 Infection"). The authors also manually screened the reference lists of reviews to guarantee that all relevant articles were included.

Two authors (YLC, WWC) independently screened out the full-text articles and included studies according to the following criteria. They reached a consensus on inclusion criteria: (1) cohort, case-control, case-series, or cross-sectional study; (2) consecutive COVID-19 patients. The exclusion criteria were: (1) patients aged $<$ 18 years, and pregnant women; (2) a sample size $<$ 10. If an institution published several similar articles, only the one with the largest sample size was included. The differences were resolved by an arbitrator (ZMC).

Data extraction and quality assessment

Data extraction and quality assessment of the included studies were conducted by two authors (DX and YYL), respectively. The data involved study design, publishing location, reasons for CTPA examination, and prophylactic anticoagulation ratio. The demographic, clinical, and laboratory features were also extracted. The study quality was assessed by the Newcastle Ottawa Score checklist (Jevnikar et al., 2020).

Statistical analysis

Weighted mean difference (WMD) with 95% confidence intervals (CI) was chosen as the effect size of a continuous variable, and odds ratio (OR) with 95% CI for a dichotomous variable. All analyses were executed using Stata MP version 14.0 (Stata Corporation, College Station, TX, USA), with heterogeneities assessed by I^2 (Jiménez et al., 2020). An I^2 of 25%, 50%, and 75% indicates low, moderate, and high heterogeneity, respectively. When $I^2 < 50\%$, inverse variance weights (fixed-effect model) were used. If $I^2 > 50\%$, the DerSimonian-Laird procedure (random-effect model) was used. At the same time, a further sensitivity analysis was performed with subgroup analyses for every parameter in three categories. According to the different study populations, the included studies were divided into: CTPA vs. COVID-19 subgroup (COVID-19 patients who were suspected of PE and underwent CTPA vs. all COVID-19 patients); unclear-ratio vs. low-ratio (ratio $<$ 80%) vs. high-ratio subgroup (ratio $>$ 80%) (the patients with different ratios of thromboprophylaxis); and the hospitalization vs. ICU-stay subgroup. The publication bias (studies $\geq$ 10) was evaluated using Egger's test (Higgins et al., 2003). $P < 0.05$ was considered as statistical significance.

Results

Study selection and quality assessment

The search strategy identified 2210 articles. After the exclusion of duplicates, 1270 articles were screened. Seventy-nine were considered eligible for full-text evaluation. Finally, 27 studies were included according to the inclusion and exclusion criteria (Figure 1). The risk of bias was judged as low for all included studies (Table 1).

Characteristics of included studies

All 27 included studies involved 927 PE patients and 3927 non-PE patients (Bompard et al., 2020, Fauvel et al., 2020, Flumignan et al., 2020, Fox et al., 2020, Grillet et al., 2020, Jalaber et al., 2020, Huisman et al., 2018, Kim et al., 2007, Kirsch et al., 2020, Konstantinides et al., 2019, Kosior et al., 2020, Kunutsor and Laukkanen, 2020, Lax et al., 2020, Léonard-Lorant and Delabranche, 2020, Liao et al., 2020, Llitjos et al., 2020, Mestre-Gómez et al., 2020, Mouhat et al., 2020, Mueller-Peltzer et al., 2020, Nopp et al., 2020, Ooi et al., 2020, Pandey and Agarwal, 2020, Planquette et al., 2021, Rodriguez-Sevilla et al., 2020, Poyiadji et al., 2020, Salje et al., 2020, Scudiero et al., 2021), of which 23 were retrospective case-control studies and four were prospective cohort studies (Fox et al., 2020, Mestre-Gómez et al., 2020, Planquette et al., 2021, Rodriguez-Sevilla et al., 2020) (Table 1). Among these studies, 24 were from Europe (833 PEs vs. 3604 non-PEs), two were from America (Fauvel et al., 2020, Kosior et al., 2020), and one was from China (Jalaber et al.,

Table 1
Characteristics of the included studies.

Study ID	Region, country	Study design	No. of COVID-19[a]	Diagnosis of COVID-19	Reasons for PE screening	Ratio[b]	No. of CTPA[c]	No.of PE[d]	Quality[e]
Fauvel C (Bompard et al., 2020)	France	retrospective, multi-center, multi-hospital	2878	RT-PCR+, clinical criteria	unexplained respiratory deterioration	67.5%	1240	103	8
Poyiadji N (Fauvel et al., 2020)	Detroit, USA	retrospective, multi-hospital	–	RT-PCR+	–	–	328	72	8
Mestre-Gómez B (Flumignan et al., 2020)	Madrid, Italy	retrospective, single non-critical ward	452	RT-PCR +, clinical criteria	unexplained respiratory deterioration, elevation of D-dimer	–	91	29	9
Alonso-Fernánde A (Fox et al., 2020)	Palma de Mallorca, Spain	prospective, single hospital	127	RT-PCR +, clinical criteria	D-dimer > 1 mg/L	96.7%	30	15	8
Fang C (Grillet et al., 2020)	London, UK	retrospective, single hospital	1200	RT-PCR+	–	–	93	41	8
Chen JP (Jalaber et al., 2020)	Wuhan, China	retrospective, single hospital	1008	15 RT-PCR+, 10 clinical criteria	elevated D-dimer, PE symptom(s)	–	25	10	9
Leonard-Lorant I (Huisman et al., 2018)	Strasbourg, France	Retr ospective, 2 hospitals	–	97 RT-PCR+, 9 clinical criteria	–	46.2%	106	32	8
Bompard F (Kim et al., 2007)	Paris, France	retrospective, 2 hospitals	–	–	respiratory deterioration	100%	135	32	8
Ooi MWX (Kirsch et al., 2020)	Greater Manchester, UK	retrospective, 5 hospitals	974	RT-PCR+, clinical criteria	respiratory deterioration, elevation of D-dimer	–	84	32	9
Ventura-Diaz S (Konstantinides et al., 2019)	Madrid, Spain	retrospective, single hospital	–	RT-PCR+, clinical criteria	–	–	242	73	8
Kirsch B (Kosior et al., 2020)	Houston, USA	retrospective, single hospital	459	–	–	–	64	12	7
Planquette B (Kunutsor and Laukkanen, 2020)	Paris, France	retrospective, 2 hospitals	–	RT-PCR +, clinical criteria	–	34.6%	269	59	8
Mouhat B (Lax et al., 2020)	Besançon, France	retrospective, single hospital	349	RT-PCR+	unexplained respiratory deterioration	87%	162	44	9
Whyte MB (Léonard-Lorant and Delabranche, 2020)	London, UK	retrospective, single hospital	–	145 RT-PCR, 69 Clinical criteria	unexplained clinical deterioration	100%	214	80	9
Grillet F (Liao et al., 2020)	Besancon Cedex, France	retrospective, single hospital	280	RT-PCR+, clinical criteria	–	–	100	23	8
Bavaro DF (Llitjos et al., 2020)	Bari, Italy	retrospective, single hospital	–	–	D-dimer > 1 mg/L and clinically suspected PE	85%	20	8	8
Benito N (Mestre-Gómez et al., 2020)	Barcelona, Spain	prospective, single hospital	1275	RT-PCR+	unexplained circulatory/ respiratory deterioration, elevation of D-dimer	88.2%	76	32	9

(*continued on next page*)

Table 1 (*continued*)

Study ID	Region, country	Study design	No. of COVID-19[a]	Diagnosis of COVID-19	Reasons for PE screening	Ratio[b]	No. of CTPA[c]	No.of PE[d]	Quality[e]
Gervaise A (Mouhat et al., 2020)	Saint Mandé, France	retrospective, single ED	–	58 RT-PCR +, 14 clinical criteria	respiratory deterioration, elevation of D-dimer	–	72	13	9
Contou D (Mueller-Peltzer et al., 2020)	Argenteuil, France	retrospective, single ICU	92	RT-PCR +	unexplained circulatory/ respiratory deterioration	100%	26	16	9
Zotzmann V (Nopp et al., 2020)	Freiburg, Germany	retrospective, single ICU	113	RT-PCR +	severe ARDS	–	20	12	9
Soumagne T (Ooi et al., 2020)	Besancon, France	retrospective, single ICU	–	RT-PCR +	respiratory deterioration	81.8%	44	17	9
Taccone FS (Pandey and Agarwal, 2020)	Brussels, Belgium	retrospective, single ICU	82	RT-PCR +	mechanical ventilation	100%	40	13	9
Jevnikar M (Planquette et al., 2021)	Le Kremlin-Bicêtre, France	prospective, multi-center, multi-hospital	135	RT-PCR +	systematic screening	–	107	16	9
Jalaber C (Rodriguez-Sevilla et al., 2020)	Saint Priest en Jarez, France	prospective, single ED	70	65 RT-PCR+, 5 clinical criteria	systematic screening	–	70	4	9
Ameri P (Poyiadji et al., 2020)	Italy	retrospective, multi-center, 13 cardiology units	689	RT-PCR +, clinical criteria	–	–	–	52	8
Lascarrou JB (Salje et al., 2020)	France and Belgium	retrospective, multi-center, 21 ICU	375	RT-PCR +	–	100%	–	55	8
Scudiero F (Scudiero et al., 2021)	Seriate, Italy	retrospective, multi-center, 7 hospitals	224	RT-PCR +	–	18.8%	–	32	8

Abbreviations: COVID-19, coronavirus disease 2019; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; RT-PCR+, positive reverse transcription-polymerase chain reaction; ICU, intensive care unit; ED, emergency department

[a] No. of COVID-19, number of patients with COVID-19

[b] Ratio, ratio of prophylactic anticoagulation

[c] No. of CTPA, number of patients with CTPA examination or suspicion of PE

[d] No. of PE, number of patients with confirmed PE

[e] Quality, all studies were assessed by the Newcastle Ottawa Score (NOS); –, not available

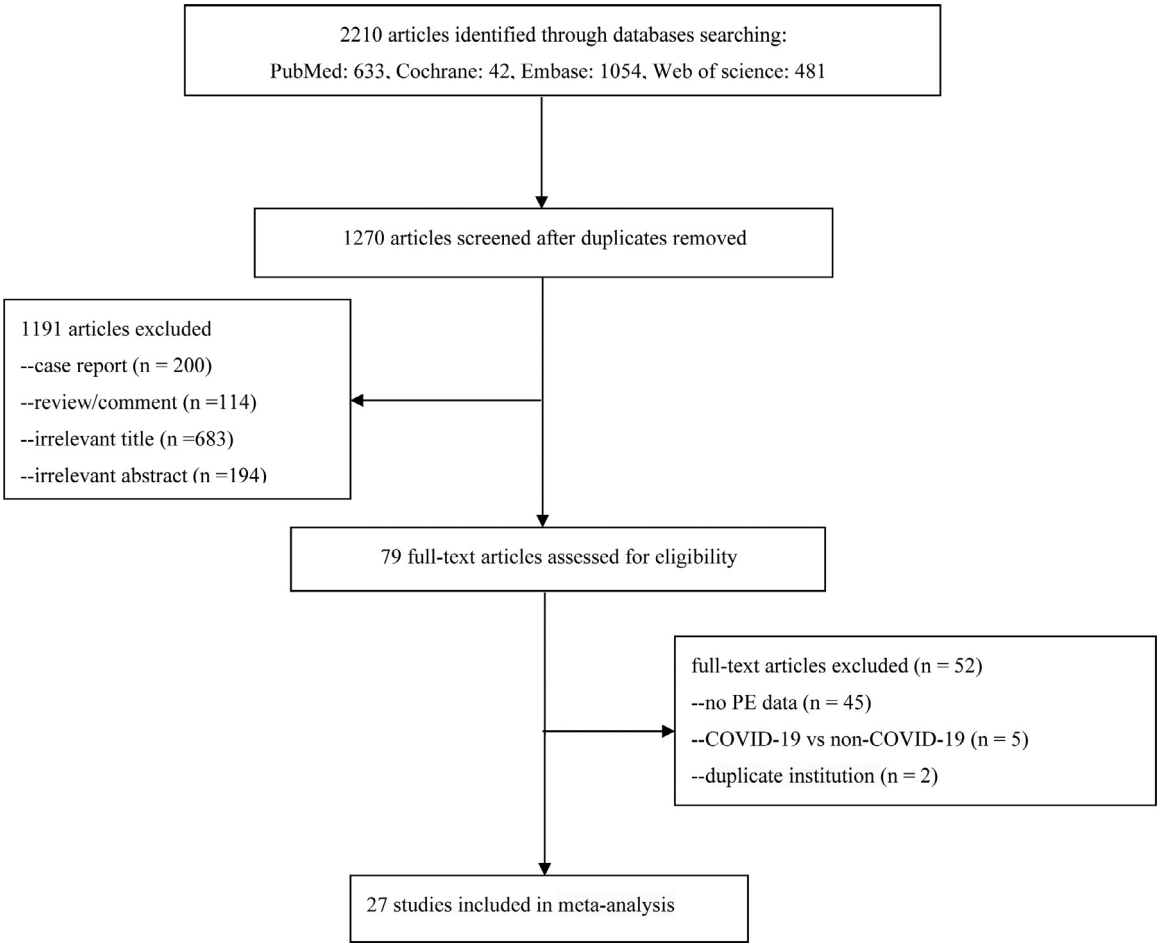

Fig. 1. Flow chart of article selection.

2020). The CTPA subgroup consisted of 22 articles involving 768 PEs and 2621 non-PEs, with 15 articles stating the reason for CTPA examination, of which unexplained respiratory deterioration or a rapid increase in D-dimer counted the most (Bompard et al., 2020, Flumignan et al., 2020, Fox et al., 2020, Jalaber et al., 2020, Kim et al., 2007, Kirsch et al., 2020, Lax et al., 2020, Léonard-Lorant and Delabranche, 2020, Llitjos et al., 2020, Mestre-Gómez et al., 2020, Mouhat et al., 2020, Mueller-Peltzer et al., 2020, Nopp et al., 2020, Ooi et al., 2020, Pandey and Agarwal, 2020) (Table 1). The COVID-19 subgroup consisted of five articles involving 159 PEs and 1306 non-PEs (Planquette et al., 2021, Rodriguez-Sevilla et al., 2020, Poyiadji et al., 2020, Salje et al., 2020, Scudiero et al., 2021). In the subgroup analysis of prophylactic anticoagulation, unclear, low-ratio (18.8–67.5%), and high-ratio (82–100%) subgroups contained 13 (389 PEs vs. 1596 non-PEs) (Fauvel et al., 2020, Flumignan et al., 2020, Grillet et al., 2020, Jalaber et al., 2020, Kirsch et al., 2020, Konstantinides et al., 2019, Kosior et al., 2020, Liao et al., 2020, Mouhat et al., 2020, Nopp et al., 2020, Planquette et al., 2021, Rodriguez-Sevilla et al., 2020, Poyiadji et al., 2020), four (226 PEs vs. 1521 non-PEs) (Bompard et al., 2020, Huisman et al., 2018, Kunutsor and Laukkanen, 2020, Scudiero et al., 2021), and 10 studies (312 PEs vs. 810 non-PEs) (Fox et al., 2020, Kim et al., 2007, Lax et al., 2020, Léonard-Lorant and Delabranche, 2020, Llitjos et al., 2020, Mestre-Gómez et al., 2020, Mueller-Peltzer et al., 2020, Ooi et al., 2020, Pandey and Agarwal, 2020, Salje et al., 2020). Eighteen studies (716 PEs vs. 2710 non-PEs) were carried on the hospitalization of the study population and five studies (113 PEs vs. 393 non-PEs) were carried on the ICU stay (Contou et al., 2020; Zotzmann et al., 2020; Soumagne and Winiszewski, 2020; Taccone et al., 2020; Soumagne and Lascarrou, 2020).

Risk factors

Demographic risk factors

Nearly all included studies reported information about age and sex. The pooled estimates indicated that males developed PE more easily than females (OR 1.49, 95% CI 1.26–1.75, $I^2 = 0.0\%$, $P = 0.000$) (Table 2, Figure 2A). Age had no significant influence on the occurrence of PE (WMD 1.57, 95% CI -0.31–3.45, $I^2 = 64.9\%$, $P = 0.101$), excluding one study by sensitivity analysis (Léonard-Lorant and Delabranche, 2020) (Table 2). Eleven studies reported information about BMI, and the pooled data showed that obesity (BMI > 30) was associated with PE occurrence (OR 1.37, 95% CI 1.03–1.82, $P = 0.033$, $I^2 = 0\%$) (Table 2, Figure 2B). Estimates for eight comorbidities were also pooled, including previous VTE, chronic heart failure, cancer, diabetes, hypertension, recent surgery, cardiovascular disease, and chronic obstructive pulmonary disease. All comorbidities were found to have no association with PE occurrence ($P > 0.068$), with low heterogeneity ($I^2 = 0–35.3\%$). Among all the demographic parameters, only age had publication bias ($P = 0.002$).

Clinical risk factors

Five studies (119 PEs vs. 266 non-PEs) reported the relationship between mechanical ventilation (MV). The result indicated that patients with MV had a significantly higher rate of PE (OR 3.34,

Table 2
Meta-analysis results of the whole studies on PE risk factors in COVID-19.

Variables	$N_{studies}$ [a]	PE, n/PE [b]	non-PE, n/non-PE [c]	WMD/OR	95% CI	I^2 (%)	*P*-value	Egger's
Demographic risk factors								
Age, years (WMD)	26	847	3793	1.57	-0.31–3.45	64.9%	0.101	**0.002**
Male, % (OR)	26	627/911	2356/3836	1.49	1.26–1.76	0.0%	**0.000**	0.606
Obesity (BMI > 30%)	11	123/329	237/706	1.37	1.03–1.82	0.0%	**0.033**	0.238
Comorbidities, % (OR)								
Previous VTE	8	47/457	168/2160	1.37	0.96–1.95	0.0%	0.079	–
Chronic heart failure	7	25/358	248/2619	0.85	0.55–1.31	35.3%	0.456	–
Cancer	13	56/530	325/2430	0.81	0.59–1.10	32.4%	0.175	0.473
Diabetes	18	146/578	746/3073	0.98	0.78–1.21	0.0%	0.819	0.136
Hypertension	17	288/599	1615/3099	0.84	0.70–1.01	0.0%	0.068	0.159
Recent surgery	3	4/126	10/389	0.97	0.30–3.12	0.0%	0.955	–
Cardiovascular disease	12	58/381	383/2573	0.95	0.69–1.32	0.0%	0.765	0.613
COPD	8	34/381	224/2466	0.91	0.62–1.35	0.0%	0.651	–
Clinical risk factors, % (OR)								
Mechanical ventilation	5	52/119	61/266	3.34	1.90–5.86	10.8%	**0.000**	–
Severe parenchymal abnormalities on chest CT (> 50%)	7	170/288	1183/1555	1.92	1.43–2.58	0.0%	**0.000**	–
ICU admission	7	118/272	177/676	2.65	1.48–4.74	66.0%	**0.001**	–
Laboratory risk factors, (WMD)								
D-dimer, ug/ml (closest to the CTPA)	10	274	634	6.03	5.14–6.92	38.0%	**0.000**	0.872
D-dimer, ug/ml (hospital admission)	9	310	2089	2.10	1.10–3.10	73.8%	**0.000**	–
WBC, × 10^9/L (closest to the CTPA)	5	216	457	1.46	0.77–2.15	0.0%	**0.000**	–
WBC, × 10^9/L (hospital admission)	3	163	1786	2.10	1.21–3.00	0.0%	**0.000**	–
Lymphocytes, × 10^9/L (closest to the CTPA)	3	38	57	-0.09	-0.62–0.43	51.6%	0.734	–
Lymphocytes, × 10^9/L (hospital admission)	4	229	1907	0.009	-0.09–0.10	0.0%	0.855	–
Fibrinogen, g/L (closest to the CTPA)	4	136	268	-0.10	-0.77–0.56	22.1%	0.759	–
Fibrinogen, g/L (hospital admission)	3	177	1270	0.27	-0.07–0.60	0.0%	0.122	–

Abbreviations: PE, pulmonary embolism; COVID-19, coronavirus disease 2019; WMD, weighted mean difference; OR, odds ratio; 95% CI, 95% confidence interval; VTE, venous thrombus embolism; COPD, chronic obstructive pulmonary disease; CT, computed tomography; WBC, white blood cells

[a] $N_{studies,}$ number of studies

[b] PE, n/PE, number of PE patients, number of PE patients with variable/number of PE patients

[c] non-PE, n/non-PE, number of non-PE patients, number of non-PE patients with variable/number of non-PE patients; I^2, index for the degree of heterogeneity; *P* value, significant at $P < 0.05$ and present in bold; Egger's, index for the degree of publication bias; –, not available

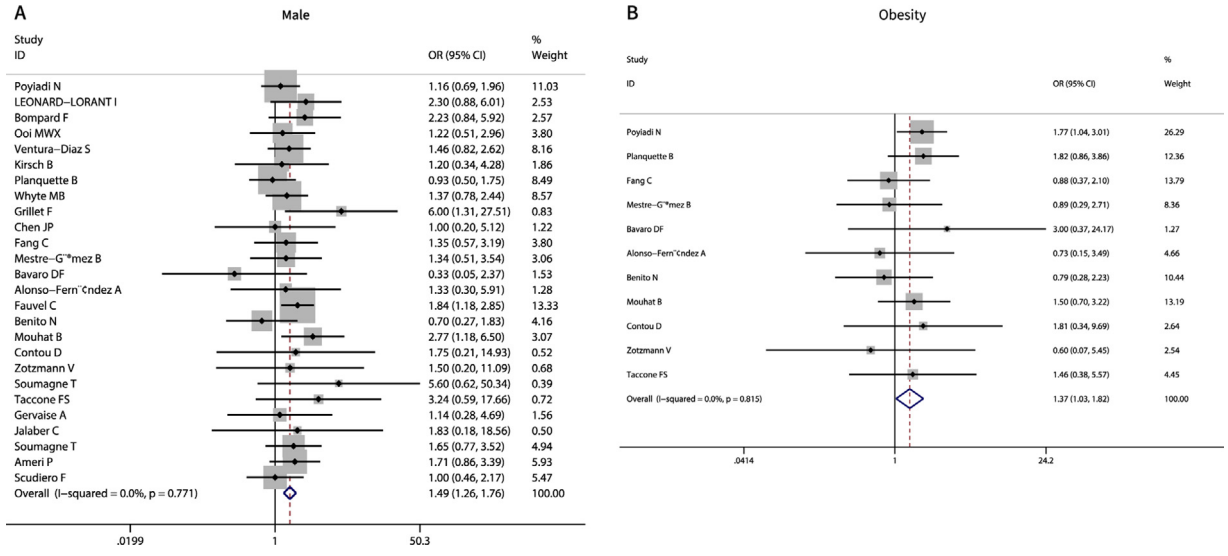

Fig. 2. Meta-analysis of demographical factors associated with PE occurrence in COVID-19. A, Male; B, Obesity.

95% CI 1.90–5.86, $P = 0.000$) with low heterogeneity ($I^2 = 10.8\%$) (Table 2, Figure 3A). Seven studies (288 PEs vs. 1555 non-PEs) evaluated the extent of parenchymal damage on chest computed tomography (CT) (Bompard et al., 2020, Grillet et al., 2020, Kim et al., 2007, Kirsch et al., 2020, Kunutsor and Laukkanen, 2020, Ooi et al., 2020, Rodriguez-Sevilla et al., 2020). The pooled estimates showed that severe parenchymal damage (> 50% of lung) had a higher PE incidence rate (OR 1.92, 95% CI 1.43–2.58, $P = 0.000$) with no heterogeneity ($I^2 = 0\%$) (Table 2, Figure 3B). The data pooled from seven studies indicated that ICU admission had a higher rate of PE than conventional wards (OR 2.65, 95% CI 1.48–4.74, $P = 0.000$), with a high heterogeneity ($I^2 = 66\%$) (Table 2, Figure 3C) (Fang et al., 2020; Léonard-Lorant et al., 2020; Bompard et al., 2020; Whyte et al., 2020; Grillet et al., 2020; Benito et al., 2020; Scudiero et al., 2021).

Laboratory risk factors

Laboratory parameters were obtained at two time points: hospital admission and closest to the CTPA examination (within 24–48 hours). The D-dimer ($P = 0.000$, $I^2 < 73.8\%$) and white blood cell (WBC) values ($P = 0.000$, $I^2 = 0\%$) in PE patients were significantly higher than that in non-PE patients at both time points (Table 2, Figure 4 A, B, C, D). Lymphocytes ($P > 0.73$, $I^2 <$

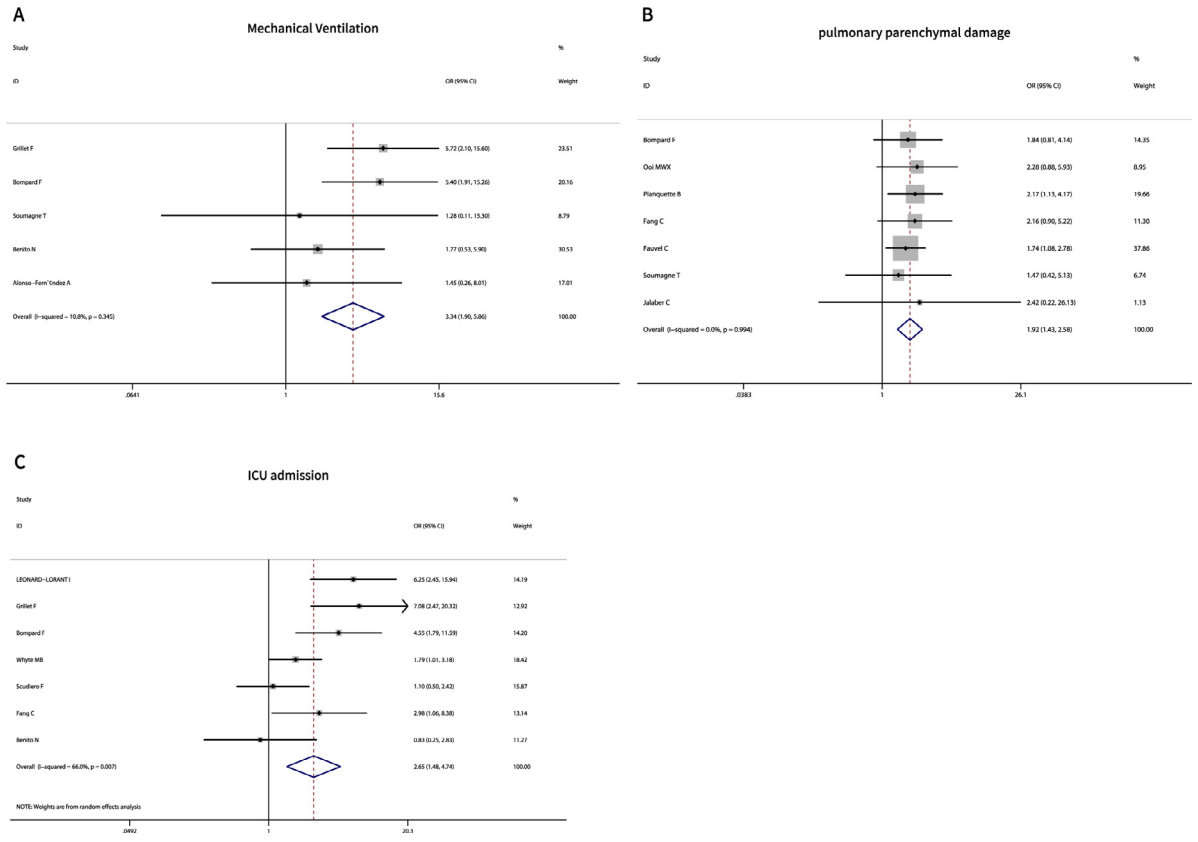

Fig. 3. Meta-analysis of clinical factors associated with PE occurrence in COVID-19. A, Mechanical Ventilation; B, pulmonary parenchymal damage; C, ICU admission.

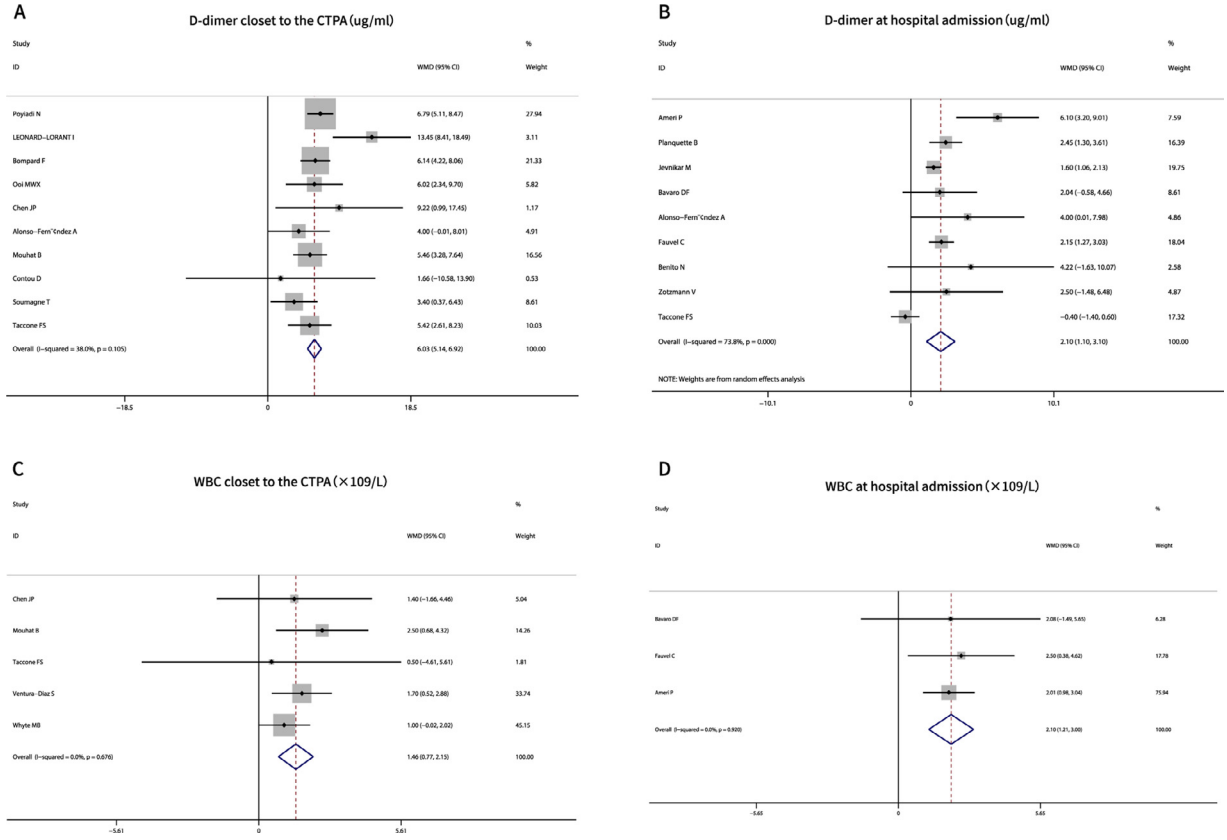

Fig. 4. Meta-analysis of laboratory factors associated with PE occurrence in COVID-19. A, D-dimer closet to the CTPA examination; B, D-dimer at hospital admission; C, WBC values closet to the CTPA examination; D, WBC values at hospital admission. Abbreviations:CTPA, computer tomography pulmonary angiography; WBC, white blood cell

51.6%) and fibrinogen ($P > 0.12$, $I^2 < 22.1\%$) had no significant influence on the occurrence of PEs, no matter at which time point (Table 2).

Subgroup analysis

There was no significant difference between the CTPA and COVID-19 subgroup ($P > 0.073$). The CTPA subgroup accounted for the majority of the included studies (22 vs. 27 studies, 768 PEs vs. 927 PEs). It had the same results as whole studies in analyses of each parameter (Supplementary Table 1). However, the COVD-19 subgroup differed from the CTPA and whole studies in males ($P = 0.072$), previous VTE ($P = 0.005$), severe parenchymal damage (> 50% of the lung) ($P = 0.468$), ICU admission ($P = 0.816$), and D-dimer value at hospital admission ($P = 0.107$) (Supplementary Table 1, Supplementary Figure 1).

Three subgroups of prophylactic anticoagulation had no difference ($P > 0.078$). Risk factors of the unclear and low-ratio subgroups were almost consistent with the results of the whole included studies, including male, MV, D-dimer (two time points), WBC (two time points), severe parenchymal damage (> 50% of the lung) ($P< 0.035$), and ICU admission ($P < 0.035$) (Supplementary Table 1). However, in the high-ratio subgroup, D-dimer (hospital admission), WBC (hospital admission), severe parenchymal damage, and ICU admission were non-risk factors ($P > 0.055$) (Supplementary Table 1).

The hospitalization subgroup, which contained 18 studies, had consistent PE risk factors with the overall studies. The ICU-stay subgroup had distinctly different results from them in age, obesity, previous VTE, hypertension, MV, severe parenchymal damage, D-dimer, and WBC (two time points) (Supplementary Table 1).

Discussion

This review analyzed several demographical, clinical, and laboratory indicators of COVID-19 patients for risk factors of PE. The whole included studies revealed that males, obesity, MV, severe parenchymal abnormalities of chest CT, ICU admission, and elevated D-dimer or WBC value (at both hospital admission and closest to CTPA) were risk factors for PE in COVID-19. Age and common comorbidities had no association with PE occurrence. PE risk factors might be different between the subgroups of these three subgroup analyses. The subgroups (the CTPA, unclear-ratio, hospitalization) that accounted for most of the included studies had consistent PE risk factors with the overall studies. Common comorbidities had no significant influence on the occurrence of PEs in all subgroups.

This systemic review revealed that risk factors for PE occurrence in COVID-19 were different from the classic risk factors. First, old age is a weak risk factor for classic PE (OR < 2), and male sex is not (Ceriani et al., 2010). However, in COVID-19, male sex was a weak risk factor (OR 1.49, $P = 0.000$) for PE occurrence, and age was not associated with PE (OR 1.57, $P = 0.101$). Second, the classic PE risk factors from comorbidities, including previous VTE with strong risk (OR > 10), chronic heart failure, cancer history with moderate risk (OR 2–9), diabetes, and hypertension with weak risk (OR < 2) (Ceriani et al., 2010) all had no association with PE in COVID-19 patients. A recent meta-analysis of risk factors for VTE in COVID-19 showed similar results to the current ones except in age (Gervaise et al., 2020). Several other studies showed that classic PE and PE in COVID-19 were different in certain characteristics (Chi et al., 2020, Choi et al., 2020, Shi et al., 2020). More interestingly, some studies stated that old age, male, and comorbidities were risk factors for severe COVID-19 (Soumagne et al., 2020, Soumagne et al., 2020) and they partly overlapped with the risk factors for PE or VTE in COVID-19. These indicate that PE or VTE in COVID-19 is affected to a certain extent by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection.

Mechanical ventilation (OR 3.72, $P = 0.000$), severe parenchymal damage (OR 1.92, $P = 0.000$), and ICU admission (OR 2.44, $P = 0.000$), which represented the severity of COVID-19 pneumonia, were associated with PE occurrence, with low heterogeneity. One imaging study found that pulmonary thrombi in COVID-19 were located in opacitated lung segments and supported this (Sungnak et al., 2020). It can also be explained by the pathological findings from autopsy: in COVID-19, distinct thrombosis and microangiopathy are common in the small vessels and pulmonary capillaries, along with classic diffuse alveolar damage (Contou et al., 2020, Egger et al., 2011, Fang et al., 2020, Taccone et al., 2020, van Dam et al., 2020). These findings are consistent with the plausible pathophysiological changes of lung lesions in COVID-19: widespread pulmonary endothelial dysfunction associated with direct viral tissue damage (ACE2 as the entry receptor for SARS-CoV-2) or immune-mediated inflammation leads to inflammatory thrombosis and microvascular dysfunction (Artifoni et al., 2020, Varga et al., 2020). Therefore, even if the pulmonary infection is also a moderate risk factor for classic PE (Ceriani et al., 2010), the new hypothesis – the etiology of PE in COVID-19 may be local microthrombosis –cannot be ruled out (Contou et al., 2020, Egger et al., 2011, Fang et al., 2020).

Elevated D-dimer and WBC levels were risk factors for PE occurrence in COVID-19 patients (at both hospital admission and closet to CTPA) ($P = 0.000$). The reason may be that they are closely related to excessive inflammation and severe COVID-19 (Soumagne et al., 2020). D-dimer has widely been deemed a marker of COVID-19-associated coagulopathy (Artifoni et al., 2020, Ventura-Diaz et al., 2020). Several studies have also proposed that D-dimer level is a good predictor for embolic events in patients with COVID-19. However, more studies are needed to assess the cut-off value, as it is inconsistent among studies (Watchmaker et al., 2020, Whyte et al., 2020, Worldometer COVID-19 Data 2020). Other studies have reported more laboratory indicators related to severe COVID-19 and VTE (Gervaise et al., 2020, Soumagne et al., 2020) than the current review, liking activated partial thromboplastin time, platelets, fibrinogen, C-reactive protein, lower lymphocyte, and so on. The reason may be that the current review separated the collection time of laboratory indicators at hospital admission or closest to the CTPA examination, which was more accurate and less heterogeneous; the small sample size may be another reason. More original articles about the clinical and laboratory characteristics of PE in detail are needed to detect the risk factors.

Although the heterogeneity of most parameters of this systematic review was low, it also performed subgroup analyses according to clinical application. Apparently, both the CTPA vs. COVID-19 and the hospitalization vs. ICU-stay subgroup analyses had distinctly different study populations. The management of thrombus in COVID-19 has always been a hot topic. Studies recommend that the use of preventive anticoagulants above conventional doses may reduce thrombotic events for patients with severe COVID-19 or those at high risk of thrombosis (Wu et al., 2020, Zeng et al., 2015). However, whether prophylactic anticoagulation should apply to all patients with COVID-19 remains controversial (Zheng et al., 2020, Zotzmann et al., 2020). Therefore, this review attempted to conduct an unclear-ratio vs. low-ratio vs. high-ratio subgroup analysis on this issue. The CTPA, unclear-ratio, or hospitalization subgroup was the group with the largest sample size in the three subgroup analyses and they had consistent results with the overall studies in low heterogeneities. This emphasized that the currently reported PE risk factors were calculated based on the population of the CTPA, unclear-ratio, or hospitalization patients. In the remaining subgroups, they had different PE risk factors, with low hetero-

geneities in most parameters. They had fewer risk factors than the CTPA, unclear-ratio, and hospitalization subgroups. While, given the vast gap in sample size between the subgroups, these differences in PE risk factors between subgroups require more evidence. Most interestingly, the three subgroup analyses only had consistent results in common comorbidities, and these traditional PE risk factors had no significant influence on the occurrence of PEs. This indicated that PE risk factors were different between COVID-19 and non-COVID-19. Moreover, PE risk factors in COVID-19 were more likely to be associated with the severity of illness, for example, MV, severe parenchymal abnormalities, ICU admission, and elevated D-dimer and WBC values.

This review had several limitations. First, due to the limitations of the original studies, several ORs had a small sample size. Also, the number of studies on COVID-19 or low-ratio subgroup was small. Fortunately, the heterogeneities of most results were acceptable. Second, 24 out of 27 included studies were from Europe, and whether the risk factors differ between regions is unclear. Third, risk factors may vary due to different subgroup analyses, and this subgroup analysis was incomplete. Subgroup analysis based on race, country, anticoagulant dose, or severity of illness can provide more comprehensive information about risk factors for PE in COVID-19. Finally, most of the included studies were retrospective case-controls. More accurate relative risks calculated from prospective cohorts are hard to obtain. Therefore, more multicenter, better-designed original studies are needed to ascertain the risk factors for PE in COVID-19 patients.

Conclusion

In conclusion, this review presented different risk factors for PE in COVID-19 from the classic risk factors in non-COVID-19. PE risk factors in COVID-19 were more likely to be associated with the severity of illness. Three subgroup analyses revealed that the currently reported risk factors for PE are mostly based on the population of COVID-19 patients with CTPA, unclear-ratio/low-ratio thromboprophylaxis, or hospitalization; these might be different in other study populations.

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Conflicts of interest

All authors declare that there are no competing interests in the research, authorship, and publication of this article.

Ethical Approval

Not applicable.

Authors’ contributions

LYC and WWC were responsible for study design, screening, data extraction, data analysis, and writing the article. And they contributed equally. ZWM, DX, and YYL helped extract and dispose of data. JYL and TWL participated in the data analysis and revision of the article. ZMC designed and revised the article.

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