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.

A systematic review and meta-analysis of incidence, prognosis, and laboratory indicators of venous thromboembolism in hospitalized patients with coronavirus disease 2019

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ABSTRACT

Objective: We have summarized the incidence, anticoagulation panels, laboratory characteristics, and mortality of venous thromboembolism (VTE) in hospitalized patients with coronavirus disease 2019 (COVID-19).

Methods: After systematically searching PubMed, Embase, the Cochrane Library, MedRxiv, and BioRxiv, a systematic review and meta-analysis of 18 retrospective, 6 prospective observational, and 2 cross-sectional studies was performed according to the guidelines of the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.

Results: Overall, 4382 hospitalized patients with COVID-19 were included. Men accounted for significantly more patients than did women (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.25-2.02; $P < .001$). The total incidence of VTE among the patients with COVID-19 was 28.3% (95% CI, 21.6%-35.4%), with an incidence of 38.0% (95% CI, 29.1%-47.4%) and 17.2% (95% CI, 11.4%-23.8%) among those with severe and general COVID-19, respectively. The total incidence of deep vein thrombosis (DVT) of the lower extremities was 18.3% (95% CI, 10.8%-27.2%). The incidence of DVT was 22.1% (95% CI, 11.0%-35.5%) and 12.8% (95% CI, 5.0%-23.3%) in those with severe and general COVID-19, respectively. The total incidence of pulmonary embolism was 17.6% (95% CI, 12.3%-23.5%), with a rate of 21.7% (95% CI, 14.8%-29.3%) in severe cases and 12.5% (95% CI, 6.1%-23.5%) in general cases. When COVID-19 severity was unclassified, the mortality for the patients with VTE was not significantly greater (25.2%; 95% CI, 12.2%-40.5%) than that for those without VTE (10.2%; 95% CI, 3.4%-19.5%; OR, 1.88; 95% CI, 0.46-7.64; $P = .377$). However, among the patients with severe COVID-19, those who had developed VTE had significantly greater mortality compared with those without VTE (OR, 2.02; 95% CI, 1.15-3.53; $P = .014$). The patients with COVID-19 and VTE had significantly higher D-dimer levels than did similar patients without VTE in multiple studies.

Conclusions: The occurrence of VTE, DVT, and pulmonary embolism has been substantial among hospitalized patients with COVID-19, especially among those with severe COVID-19. Patients with severe COVID-19 and VTE had significantly greater mortality compared with similar patients without VTE. An increased D-dimer level might be an indicator of the occurrence of VTE in patients with COVID-19. (J Vasc Surg Venous Lymphat Disord 2021;9:1099-111.)

Keywords: COVID-19; D-dimer; Deep vein thrombosis; Pulmonary embolism; Venous thromboembolism

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major health concern worldwide.[1] COVID-19 is a highly infectious disease that has been intensively evolving and is associated with high mortality.[2] In addition to attacking the respiratory system, the novel virus infects the heart, blood vessels, and kidneys by binding to angiotensin I converting enzyme 2 and, thereby, causing acute cardiovascular and/or renal injury.[3,4] The effects of COVID-19 on nonrespiratory organs partly explain why patients with severe COVID-19 often have multiorgan comorbidities.[4]

Emerging evidence has shown that COVID-19 is a vascular disease. First, the SARS-CoV-2 virus can directly invade vascular endothelial cells, leading to endothelial injury.[5] Moreover, the hypercoagulable state has been well-recognized in patients with COVID-19, with elevated circulating level of procoagulant factors, including factor VIII and fibrinogen, reported in those with severe COVID-19.[6,7] Consequently, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs often in hospitalized COVID-19 patients, especially among immobilized elderly patients.[8] Klok et al[9] reported VTE in 27% of severe COVID-19 patients, although all had received antithromboembolic prophylaxis. Cui et al[10] reported DVT of the lower extremities in 25% of severe COVID-19 patients who had not received prophylaxis. An autopsy study of 12

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consecutive patients who had died of COVID-19 found DVT in both legs of 7 patients (58.3%), 4 of whom (33.3%) had died directly of PE.[11]

The overall incidence of VTE among hospitalized COVID-19 patients is unknown owing to the heterogeneity of the studies. A systematic summary of the current evidence regarding the consequential complications of COVID-19 infection is warranted to guide clinical management. We have reported the results from a systematic review and meta-analysis of the incidence, anticoagulation panels, mortality, and laboratory characteristics of VTE among hospitalized patients with COVID-19.

METHODS

Search strategy. The analysis was performed in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.[12] A thorough search of the relevant literature was performed using PubMed, Embase, the Cochrane Library, MedRxiv, and BioRxiv from the date of the first publication of VTE occurrence in COVID-19 patients to October 12, 2020. Using a combination of MeSH terms and random words, the retrieval strategy was ("venous thromboembolism" OR VTE OR "deep vein thrombosis" OR "deep venous thrombosis" OR DVT OR "pulmonary embolism" OR PE) AND (COVID-19 OR "coronavirus disease 2019"). No language restriction was set. Paper documents were manually searched, and the references of relevant review and included literature were screened.

Literature screening. COVID-19 was classified as mild, moderate, severe, or critical using "The Diagnosis and Treatment of COVID-19 Guidelines," fifth version.[13] Patients with mild or moderate COVID-19 (hospitalized only in general wards) were defined as having general COVID-19. Patients who had been admitted to an intensive care unit (ICU) or had been described in the studies as having severe COVID-19 were defined as having severe COVID-19. Patients who had been referred to critical care units were defined as having critical COVID-19 and were included in the severe group in the present study. The patients included in the present study had to have been hospitalized with general or severe COVID-19. At least one of the following indexes were required to have been reported for study inclusion: the incidence of VTE, DVT, and/or PE; and/or D-dimer level, lymphocyte count, fibrinogen, prothrombin time, and/or mortality for VTE and no-VTE patients. The pooled incidence of VTE was defined as the incidence of all VTE, DVT, or PE cases reported in the studies. DVT was defined as thrombosis in the upper or lower extremities (thrombosis in the popliteal and/or femoral veins was defined as proximal DVT and calf vein thrombosis below the knee as distal DVT).[14] PE was classified as central (main, truncular, and lobar pulmonary artery) or peripheral (segmental and subsegmental pulmonary artery) type as described previously.[15] Observational and randomized controlled studies were included. All the included reports were original studies. The exclusion criteria were as follows: (1) studies reporting merely arterial thrombosis; (2) secondary research, including reviews and commentaries; (3) brief rapid reports, research letters, case reports, and case series; (4) replicated publications or identical data used in multiple reports (only the report containing the most complete information was included); and (5) studies that had not specified the severity of COVID-19.

Data extraction and quality evaluation. Two of us (Y.D.L., J.W.C.) independently screened the studies using the inclusion and exclusion criteria. The titles and abstracts of the reports were assessed first, with the full text then reviewed to determine inclusion. The included studies were independently extracted by the same two investigators for the following: first author's name, type of publication, study design, country, study duration and year, subject age and gender, methods used for diagnosis of COVID-19 and VTE, state of the illness, DVT location, VTE history, timing of VTE presentation, laboratory indicators (ie, blood D-dimer level, lymphocyte count, fibrinogen, prothrombin time), anticoagulation panels, and mortality. The extracted information was independently documented using a standardized form by the two investigators. Any disagreements between them was settled by consultation with, or if necessary by the decision of, a third author (L.F.Q.).

The quality of the retrospective and prospective cohort studies was assessed using the Newcastle-Ottawa scale.[16] The Newcastle-Ottawa scale includes eight scoring items: selection (four items; full score is one point per item), comparability of the cohort (one item; full score is two points), and outcome (three items; full score is one point per item). Thus, studies with a score of seven or more were defined as high-quality research. Those with a score of four to six were defined as medium-quality research, and those with a score of three or less were defined as low-quality research. The quality of the cross-sectional studies was evaluated using the scale recommended by the U.S. Agency for Healthcare Research and Quality.[17] The scale includes 11 items, which are answered as "yes" (one point), "no" (zero points), or "unclear" (zero points). A total score of 0 to 3, 4 to 7, or 8 to 11 was defined as low-, medium-, or high-quality research, respectively.

Statistical analysis. The incidence, with the 95% confidence intervals (CIs), was used to demonstrate the epidemiology of VTE in the included studies. In the comparison between those with and without VTE, a

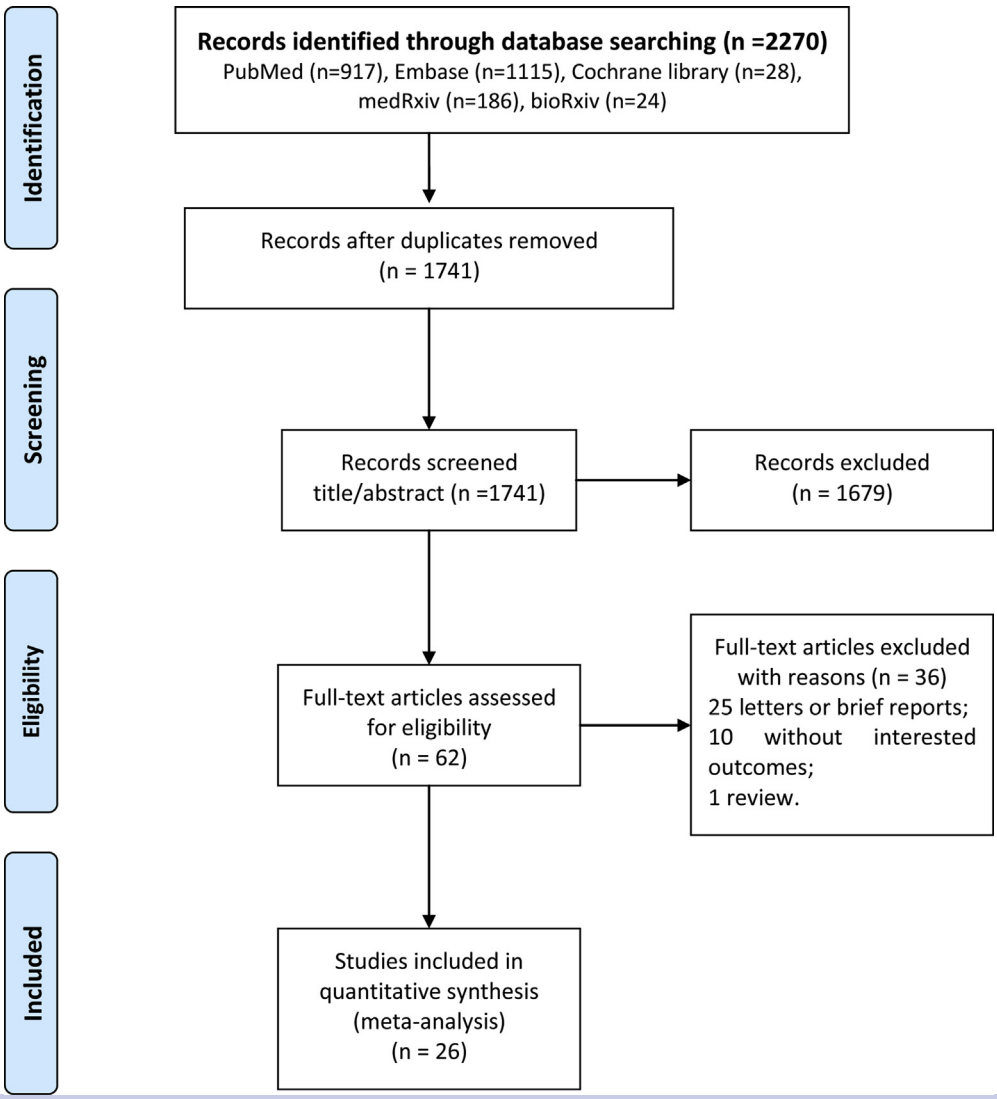

Fig 1. PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow diagram showing literature screening.

categorical variable was calculated using the odds ratios (ORs), with the 95% CIs, for a combination of the effect size. Continuous variables were calculated as the weighted mean difference with the 95% CIs. The heterogeneity of the included studies was analyzed using the Cochran Q test and I^2 statistic.[18] If the P value was $< .05$ using the Cochran Q test and/or the I^2 value was $>50\%$, the included studies were considered to have significant heterogeneity, and a random effects model was used to pool the results. If P the value was $\geq .05$ and the I^2 value was $\leq 50\%$, a fixed effects model was used. Egger's test was used to determine whether the included studies that had reported the mortality of the VTE and no-VTE groups had had a significant publication bias. All the statistical analyses were performed using Stata, version 11.0, software (StataCorp, College Station, Tex).

RESULTS

The search of the databases identified 2270 reports. After the duplicate studies had been removed and the titles and abstracts screened, 62 studies remained, and the full text of these was reviewed for eligibility. Of the 62 studies, 36 were excluded, of which 26 were letters, brief reports, or reviews and 10 contained none of the outcomes of interest. Thus, 26 studies were included in the present meta-analysis (Fig 1; PRISMA diagram). No additional studies was identified through the manual search.

All 26 studies were observational studies, of which 18 were retrospective,[9,19-35] 2 were cross-sectional and descriptive,[36,37] and 6 were prospective.[38-43] The 26 studies included 4382 patients. The demographics and descriptive information of the included studies are summarized in Table I. The study periods across the

Table I. Characteristics of 26 included studies

Investigator	Study type	Study period	COVID-19 diagnostic criteria	Outcome	Outcome definition	Age, years[a]	Patients, No.	Gender (M; F)	COVID-19 severity
Al-Samkari et al,[19] USA	RS	3/1-4/5/20	Positive result on RT-PCR of nasopharyngeal swab, oropharyngeal swab, or sputum specimen	VTE	Radiographically confirmed	65 (32-97)	144	93; 51	Severe
						60 (23-99)	256	135; 121	General
Aleva et al,[37] the Netherlands	CSS	3/9-6/20/20	Positive result on RT-PCR of nasopharyngeal swab or lower respiratory tract specimen	VTE (DVT, PE)	NR	65 (33-82)	50	33; 17	Severe
Alonso-Fernandez et al,[38] Spain	POS	4/6-4/17/20	WHO guidelines[b]	PE	CTPA	64.5 (55.8-71.3)	30	19; 11	General
Artifoni et al,[20] France	RS	3/25-4/10/20	Positive result on RT-PCR of nasopharyngeal swab specimens or typical presentation on chest CT	VTE (DVT, PE)	CTPA or CDUS	64 (46.0-75)	71	43; 28	General
Avruscio et al,[39] Italy	POS	3/4-4/30/20	Positive result on RT-PCR of nasopharyngeal or sputum specimen	VTE (DVT, PE)	CTPA, CDUS, autopsy, or clinical basis	67 (11)	41	33; 8	Severe
						67 (14)	44	28; 16	General
Chen et al,[21] China	RS	2/1/20-3/20/20	WHO guidelines[b]	DVT	CDUS	63 (55-71)	88	54; 34	Severe
Contou et al,[22] France	RS	3/13-4/24/20	Positive result on RT-PCR	PE	CTPA	63 (47-77)	26	22; 4	Severe
Demelo-Rodriguez et al,[40] Spain	POS	4/1-4/15/20	Positive PCR result of nasopharyngeal swab or radiologic and analytical findings	DVT	CDUS	68.1 (15.4)	156	102; 54	General
Dujardin et al,[23] the Netherlands	RS	3/13-4/9/20	Positive result on RT-PCR of a nose or throat swab or tracheal aspirate	VTE (DVT, PE)	CTPA or CDUS	62 (55-70)	127	98; 29	Severe
Fauvel et al,[24] France	RS	2/26-4/20/20	WHO guidelines[b]	PE	CTPA	64 (17)	1240	721; 519	General
Helms et al,[41] France	POS	3/3-3/31/20	NR	VTE (DVT, PE)	CTPA	63 (53-71)	150	122; 28	Severe
Jimenez-Guiu et al,[42] Spain	POS	4/2020	Positive result on RT-PCR of nasopharyngeal specimens	DVT	CDUS	71.3 (12.7)	57	29; 28	General
Klok et al,[9] the Netherlands	RS	3/7-4/5/20	NR	VTE (DVT, PE)	CTPA or CDUS	64 (12)	184	139; 45	Severe

Table I. Continued.

Investigator	Study type	Study period	COVID-19 diagnostic criteria	Outcome	Outcome definition	Age, years[a]	Patients, No.	Gender (M; F)	COVID-19 severity
Le Jeune et al,[25] France	RS	4/8-5/12/20	Positive result on RT-PCR of nasopharyngeal swab	VTE (DVT, PE)	CTPA or CDUS	65 (19)	42	23; 19	General
Lodigiani et al,[26] Italy	RS	2/13-4/10/20	Laboratory-proven COVID-19	VTE (DVT, PE)	CTPA or CDUS	66 (55-85)	61	264; 124	Severe
							327		General
Longchamp et al,[27] Switzerland	RS	3/8-4/4/20	Positive result on RT-PCR of nasopharyngeal swab, sputum, or bronchial aspirate	VTE (DVT, PE)	CTPA or CDUS	68 (11)	25	16; 9	Severe
Longhitano et al,[43] Italy	POS	5/18-5/30/20	Clinical features of COVID-19 and positive PCR result of nasopharyngeal swab	VTE	CTPA or CDUS	60.2 (10.5)	18	15; 3	Severe
						71.5 (15.5)	56	29; 27	General
Maatman et al,[28] USA	RS	3/12-3/31/20	Laboratory-proven COVID-19	VTE (DVT, PE)	CDUS	61 (16)	109	62; 47	Severe
Mestre-Gomez et al,[29] Spain	RS	3/20-4/12/20	WHO guidelines[b]	PE	CTPA	64.5 (57-75)	91	62; 29	General
Middeldorp et al,[30] the Netherlands	RS	3/2-4/12/20	Positive result on RT-PCR of nose/throat swab or sputum specimen	VTE (DVT, PE)	CTPA or CDUS	62 (10)	75	58; 17	Severe
						60 (16)	123	72; 51	General
Mouhat et al,[31] France	RS	3/15-4/16/20	Positive result on RT-PCR of nasal and pharyngeal swabs	PE	CTPA	65.57 (13.0)	68	109; 53	Severe
							94		General
Shah et al,[32] UK	RS	3/15-5/5/20	Positive result on RT-PCR or clinical features of COVID-19 with radiologic lesions	VTE (DVT, PE)	CTPA or CDUS	57 (49-64)	187	124; 63	Severe
Taccone et al,[33] Belgium	RS	3/10-4/30/20	Positive result on RT-PCR of nasopharyngeal swab and/or bronchoalveolar lavage specimens	PE	CTPA	61 (57-66)	40	28; 12	Severe
Trigonis et al,[34] USA	RS	3/23-4/8/20	NR	DVT	CDUS	60.8 (14.9)	45	NR	Severe
Whyte et al,[35] UK	RS	3/3-5/7/20	Positive result on RT-PCR of nasopharyngeal swabs	PE	CTPA	61.1 (15)	78	129; 85	Severe
							136		General

(Continued on next page)

Table I. Continued.

Investigator	Study type	Study period	COVID-19 diagnostic criteria	Outcome	Outcome definition	Age, years[a]	Patients, No.	Gender (M; F)	COVID-19 severity
Zhang et al,[36] China	CSS	1/29-2/29/20	WHO guidelines[b]	DVT	CDUS	63 (14)	65	74; 69	Severe
							78		General

CDUS, Compression duplex ultrasonography; *COVID-19*, coronavirus disease 2019; *CSS*, cross-sectional study; *CTPA*, computed tomography pulmonary angiography; *DVT*, deep vein thrombosis; *F*, female; *M*, male; *NR*, not reported; *PCR*, polymerase chain reaction; *PE*, pulmonary embolism; *POS*, prospective observational study; *RS*, retrospective study; *RT-PCR*, reverse transcriptase-polymerase chain reaction; *VTE*, venous thromboembolism.
[a]Presented as median (interquartile range), mean (range), or mean (standard deviation).
[b]Severe acute respiratory syndrome coronavirus 2 infection was determined by positive results from real-time RT-PCR of nasal and pharyngeal swabs or lower respiratory tract aspirates (confirmed cases) or was determined by typical imaging characteristics on chest computed tomography when laboratory test results were inconclusive (probable cases).

studies ranged from January 29, 2020 to October 12, 2020. The included studies were from France, the United States, China, the United Kingdom, Spain, Italy, and the Netherlands. COVID-19 had most often been diagnosed using the polymerase chain reaction assay of nasopharyngeal swab specimens, chest computed tomography, or chest radiographs. VTE had most often been diagnosed using computed tomography pulmonary angiography for PE and duplex ultrasonography for DVT of the extremities. The DVT and PE locations are summarized in Table II. Eight studies reported proximal and distal DVT of the lower extremities,[20,21,25,26,30,39,40,42] and two studies did not report on distal DVT.[9,27]

The weighted mean age of the patients was 64.5 years (95% CI, 57.0-71.5), with men accounting for 63.1% of the study population. The gender distribution among the hospitalized COVID-19 patients was reported in 13 studies, of which 7 had included severe COVID-19 patients and 7 had included general COVID-19 patients. No significant heterogeneity was found among the studies, and the fixed effects model was used to pool the results. The overall proportion of men was significantly greater than that of women (OR, 1.59; 95% CI, 1.25-2.02; $P < .001$). Furthermore, male patients had accounted for significantly more cases of severe or general COVID-19 than did female patients (OR, 1.61; 95% CI, 1.17-2.23; vs OR, 1.55; 95% CI, 1.08-2.22; $P = .004$ and $P = .016$, respectively).

The type of participants, detailed anticoagulation panels, VTE history, and presence of VTE at admission are summarized in Supplementary Table I (online only). The anticoagulation panels for VTE in the included studies could be summarized as standard prophylactic anticoagulation, intermediate anticoagulation, or complete anticoagulation. A total of 182 patients had a positive VTE history before admission. Except for three patients in the study by Alonso-Fernandez et al,[38] two in the study by Maatman et al,[28] and nine in the study by Mouhat et al,[31] who had had VTE at admission, all the patients in the included studies with VTE had developed VTE after hospitalization. The patients who had received standard prophylactic anticoagulation alone had a greater pooled incidence of VTE, DVT, and PE than did those who had received mixed anticoagulation. However, the difference was not significant (Supplementary Table II, online only). The methodologic quality of each study was medium.

VTE incidence in hospitalized COVID-19 patients. The incidence of VTE among the hospitalized COVID-19 patients was reported in 26 studies with 34 patient cohorts. The studies had significant heterogeneity, and the random effects model was used to pool the results. The overall VTE incidence among the hospitalized COVID-19 patients was 28.3% (95% CI, 21.6%-35.4%). For the hospitalized patients with severe COVID-19 (19 cohorts), the incidence was 38.0% (95% CI, 29.1%-47.4%), and for those with general COVID-19 (15 cohorts), the incidence was 17.2% (95% CI, 11.4%-23.8%; Fig 2).

DVT incidence in hospitalized COVID-19 patients. The incidence of DVT among hospitalized COVID-19 patients was reported in 17 studies, with 21 patient cohorts. The studies had significant heterogeneity; thus, the random effects model was used to pool the results. The overall DVT incidence among the hospitalized COVID-19 patients was 18.3% (95% CI, 10.8%-27.2%). The incidence of proximal DVT of lower extremities was 4.5% (95% CI, 1.4%-8.8%) and that of distal DVT was 9.2% (95% CI, 3.5%-17.1%). For the severe COVID-19 patients (13 cohorts), the incidence of DVT was 22.1% (95%CI 11.0-35.5), with an incidence of proximal DVT of the lower extremities of 9.9% (95% CI, 1.1-24.6) and of distal DVT of 14.6% (95% CI, 3.1%-31.8%). For the general COVID-19 patients (eight cohorts), the incidence of DVT was 12.8% (95% CI, 5.0%-23.3%). The incidence of proximal DVT of the lower extremities was 1.1% (95% CI, 0.3%-2.2%) and that of distal DVT was 6.6% (95% CI, 1.7%-14.0%; Fig 3).

PE incidence in hospitalized COVID-19 patients. The incidence of PE among the hospitalized COVID-19 patients was reported in 19 studies, with 24 patient cohorts. The studies had significant heterogeneity; thus, the random effects model was used to pool the results. The overall PE incidence for the hospitalized COVID-19

Table II. Studies reporting location of deep vein thrombosis (*DVT*) and pulmonary embolism (*PE*)

Investigator	Outcome	COVID-19 severity	DVT and PE location
Artifoni et al[20]	VTE (DVT, PE)	General	Proximal DVT of lower extremities, 2; distal DVT of lower extremities, 5
Avruscio et al[39]	VTE (DVT, PE)	Severe	DVT of internal jugular vein, 3; proximal DVT of lower extremities, 8; distal DVT of lower extremities, 6; DVT of upper extremities, 9
Avruscio et al[39]	VTE (DVT, PE)	General	DVT of internal jugular vein, 4; proximal DVT of lower extremities, 2; distal DVT of lower extremities, 4
Chen et al[21]	DVT	Severe	Universal DVT, 8; distal DVT of lower extremities, 32
Contou et al[22]	PE	Severe	Main PE, 4; lobar PE, 2; segmental PE, 10
Demelo-Rodriguez et al[40]	DVT	General	Proximal DVT of lower extremities, 1; distal DVT of lower extremities, 22
Helms et al[41]	VTE (DVT, PE)	Severe	Truncular PE, 9; lobar PE, 8; segmental PE, 5; subsegmental PE, 3
Jimenez-Guiu et al[42]	DVT	General	Proximal DVT of lower extremities, 1; distal DVT of lower extremities, 5
Klok et al[9]	VTE (DVT, PE)	Severe	Proximal DVT of lower extremities, 1; DVT of upper extremities, 2; segmental PE, 18; subsegmental PE, 7
Le Jeune et al[25]	VTE (DVT, PE)	General	Proximal DVT of lower extremities, 1; distal DVT of lower extremities, 7
Lodigiani et al[26]	VTE (DVT, PE)	Severe	Proximal DVT of lower extremities, 1; DVT of upper extremities, 1
		General	Proximal DVT of lower extremities, 3; distal DVT of lower extremities, 1; lobar PE, 2; segmental PE, 3; subsegmental PE, 1
Longchamp et al[27]	VTE (DVT, PE)	Severe	Proximal DVT of lower extremities, 6; lobar PE, 3; segmental PE, 2
Mestre-Gomez et al[29]	PE	General	Central PE, 9; peripheral PE, 20
Middeldorp et al[30]	VTE (DVT, PE)	Severe	Proximal DVT of lower extremities, 14; distal DVT of lower extremities, 9; DVT of upper extremity, 1; lobar PE, 1; segmental PE, 9; subsegmental PE, 1
Taccone et al[33]	PE	General	Distal DVT of lower extremities, 2; segmental PE, 1; subsegmental PE, 1
		Severe	Proximal PE, 2; subsegmental PE, 1; segmental PE, 10

COVID-19, Coronavirus disease 2019; *VTE*, venous thromboembolism.

patients was 17.6% (95% CI, 12.3%-23.5%). The overall incidence of central PE was 6.8% (95% CI, 1.8%-14.2%) and that of peripheral PE was 12.3% (95% CI, 6.1%-20.2%). The PE incidence for the severe COVID-19 patients (14 cohorts) was 21.7% (95% CI, 14.8%-29.3%). The incidence of central PE in the severe COVID-19 group was 8.5% (95% CI, 2.7%-16.6%) and that of peripheral PE was 16.3% (95% CI, 9.5%-24.4%). The PE incidence for the hospitalized patients with general COVID-19 (10 cohorts) was 12.5% (95% CI, 6.1%-23.5%), with an incidence of central PE of 1.7% (95% CI, 0.6%-3.3%) and peripheral PE of 6.4% (95% CI, 0.4%-17.8%; Fig 4).

Comparison of mortality and laboratory indicators in VTE and no-VTE groups. The mortality rate for COVID-19 patients with and without VTE was reported in eight studies, with five severe and four general COVID-19 cohorts. Significant heterogeneity existed among the studies; thus, the random effects model was used to pool the results. The numeric difference in mortality for those with unclassified COVID-19 with VTE (25.2%; 95% CI, 12.2%-40.5%) and without VTE (10.2%; 95% CI, 3.4%-19.5%) was not statistically significant (OR, 2.06; 95% CI, 1.00-4.25; $P = .05$). Furthermore, no statistically significant difference was found between the general COVID-19 patients with and without VTE (OR, 4.59; 95% CI, 0.30-70.29; $P = .274$). However, severe COVID-19 patients with VTE had a significantly greater mortality rate (38.1%; 95% CI, 24.7%-52.4%) compared with those with severe COVID-19 but without VTE (22.0%; 95% CI, 9.4%-37.5%; OR, 2.02; 95% CI, 1.15-3.53; $P = .014$; Fig 5).

The blood levels of D-dimer, lymphocytes, fibrinogen, and prothrombin time of the VTE and no-VTE patients are listed in Supplementary Table III (online only). These indicators had a non-Gaussian distribution; thus, a meta-analysis was not performed. The D-dimer levels were significantly higher in the patients with VTE than in those without VTE in 13 of the included studies[20,21,24,28,29,31-36,40,43] ($P < .05$). The lymphocyte count was significantly lower in the patients with VTE than in those without VTE in two of the included studies[31,36] ($P < .05$). The prothrombin time was longer in the patients with VTE than in those without VTE in the one included study that had reported the prothrombin time ($P < .05$).[36]

Test of publication bias. The incidence across the studies was not subjected to a test of publication bias. The mortality rates and gender distribution of the VTE and no-VTE groups were analyzed using the Egger test.

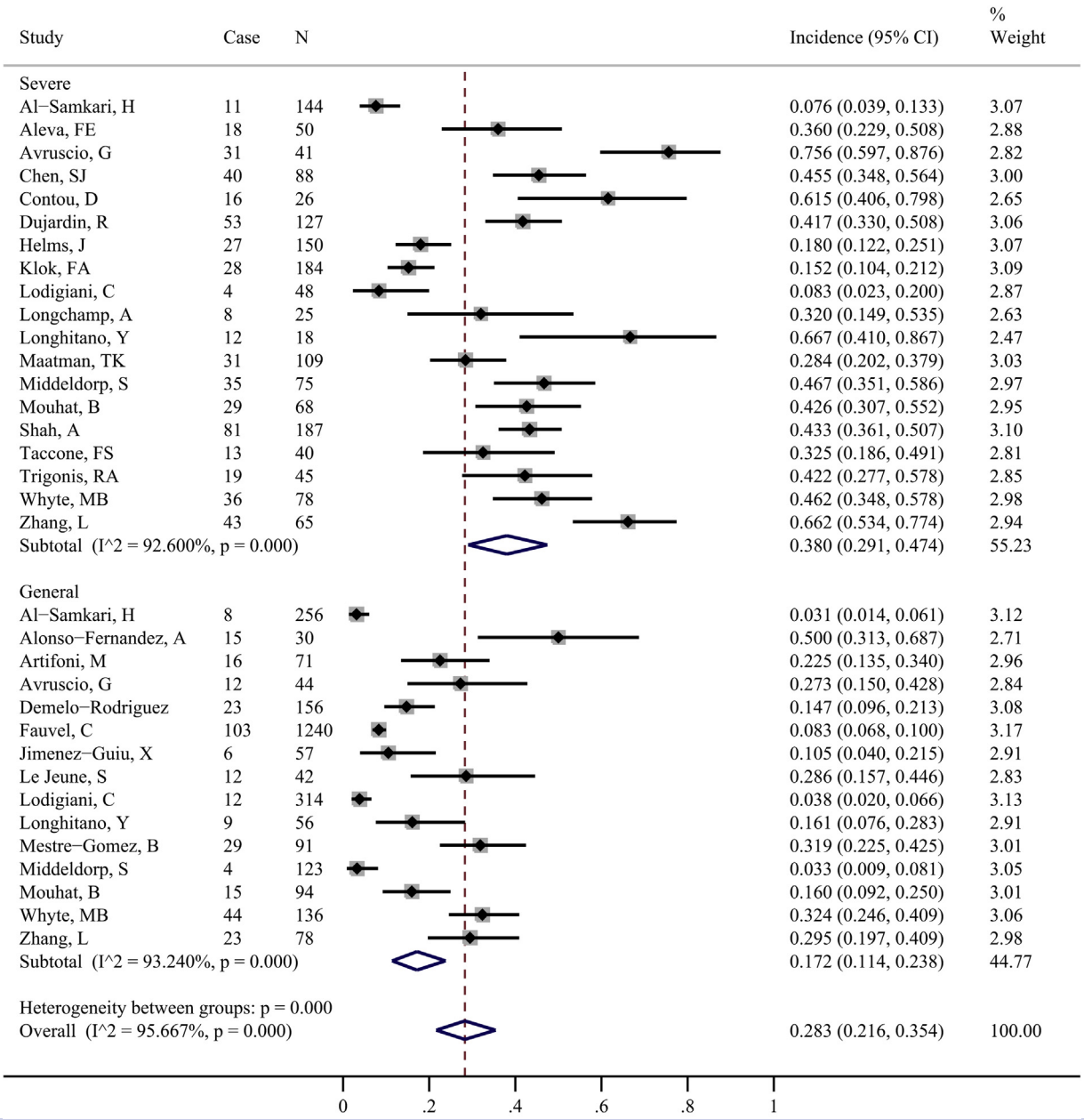

Fig 2. Forest plot representing overall incidence of venous thromboembolism (VTE) among severe and general hospitalized coronavirus disease 2019 (COVID-19) patients. The pooled prevalence rate of VTE was 28.3%. The *gray squares* indicate the weights used in the meta-analysis. *Case,* Cases of VTE; *CI,* confidence interval; *N,* total number of patients.

No significant bias for either was found (mortality rate, $t = 2.15$; $P = .075$; gender distribution, $t = 0.53$; $P = .606$).

DISCUSSION

A comprehensive meta-analysis of the incidence and mortality of VTE among those with general or severe COVID-19 was performed. Twenty-six studies with 4382 patients were included, and 20 of the studies had had >50 patients. The overall VTE incidence was 28.3% among the hospitalized COVID-19 patients, with an incidence of 38.0% among those with severe COVID-19. The overall incidence of DVT was 18.3%, and the DVT incidence among the hospitalized severe COVID-19 patients was 22.1%. The overall incidence of PE was 17.6%, and the PE incidence among the hospitalized severe COVID-19 patients was 21.7%. These results highlight that the incidence of thrombotic events among hospitalized patients with COVID-19 is

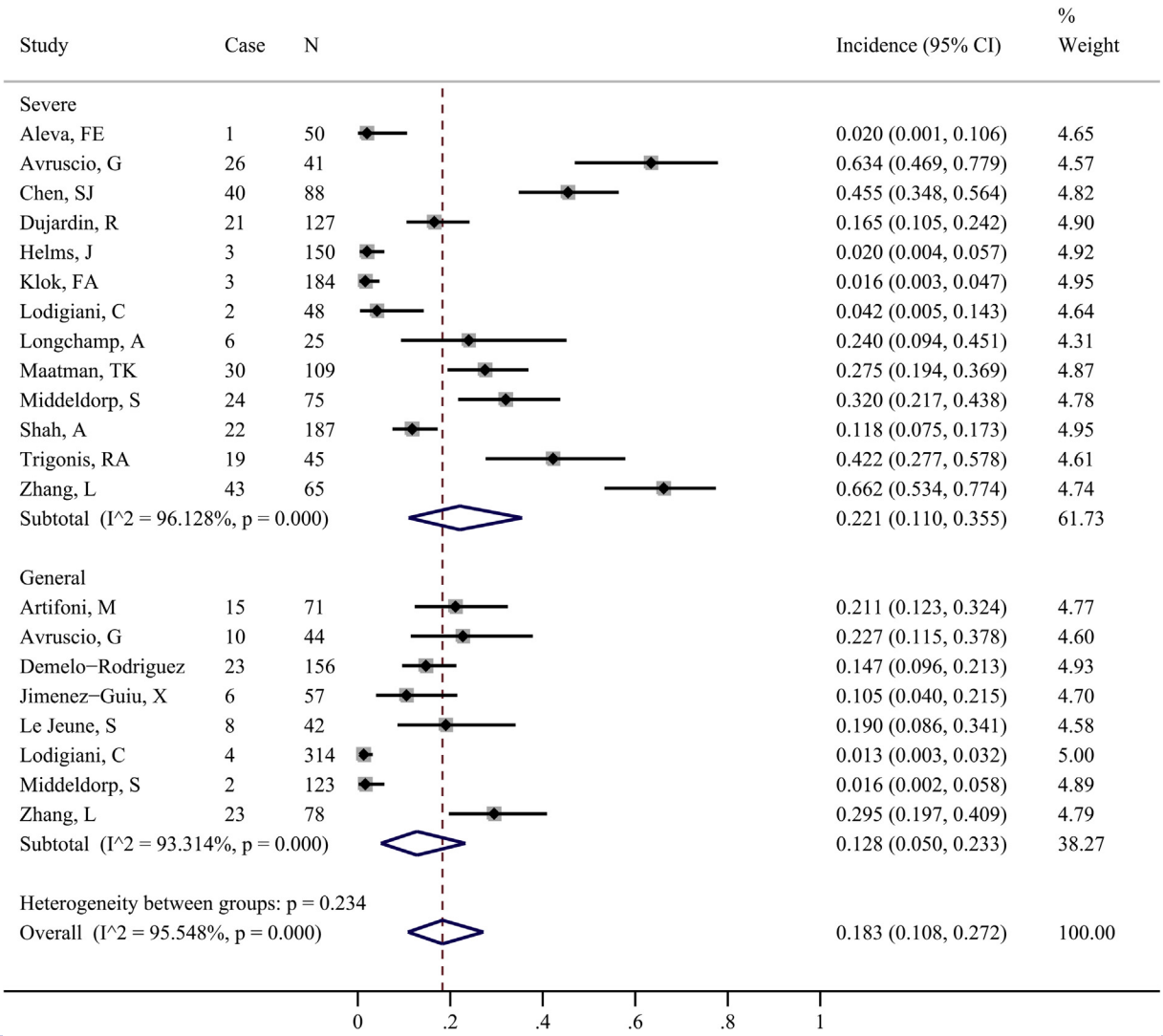

Fig 3. Forest plot representing overall incidence of deep vein thrombosis (DVT) among severe and general hospitalized coronavirus disease 2019 (COVID-19) patients. The pooled prevalence rate of DVT was 18.3%. The *gray squares* indicate the weights used in the meta-analysis. *Case,* Cases of DVT; *CI,* confidence interval; *N,* total number of patients.

considerable and is especially high among those with severe COVID-19.

Male dominance (63.1%) was observed among the hospitalized COVID-19 patients. In the severe and general subgroups, the proportion of men was greater than that of women, which might indicate a significant association between male gender and COVID-19 infection. Additionally, male gender could be a risk factor for VTE. A multicenter cohort study found that male gender were significantly associated with PE,[24] and a recent retrospective study found male gender independently associated with the occurrence of DVT.[44] Whether these associations reflect the deleterious effects of androgen on vessel walls, characterized by impaired endothelial function, is unknown but deserving of consideration.[45] COVID-19 damages the vascular endothelial cells and causes hypercoagulability. Therefore, male gender could be a risk factor for VTE, especially in the context of COVID-19.

The overall incidence of VTE in the present meta-analysis was inconsistent with other recently reported meta-analyses. Lu et al[46] performed a meta-analysis of VTE event in patients with COVID-19 from 20 original studies. They reported that the overall VTE, PE, and DVT incidence was 21%, 15%, and 27%, respectively.[46] Another meta-analysis of 12 studies reported that the overall incidence of VTE among severe COVID-19 patients was 31%.[47] However, these studies did not differentiate the VTE incidence between general and severe COVID-19 cases. We believe the data from our study are more precise and unbiased, because more original studies were included in the analysis. Furthermore, the VTE incidence in COVID-19 patients was subjected to a subgroup

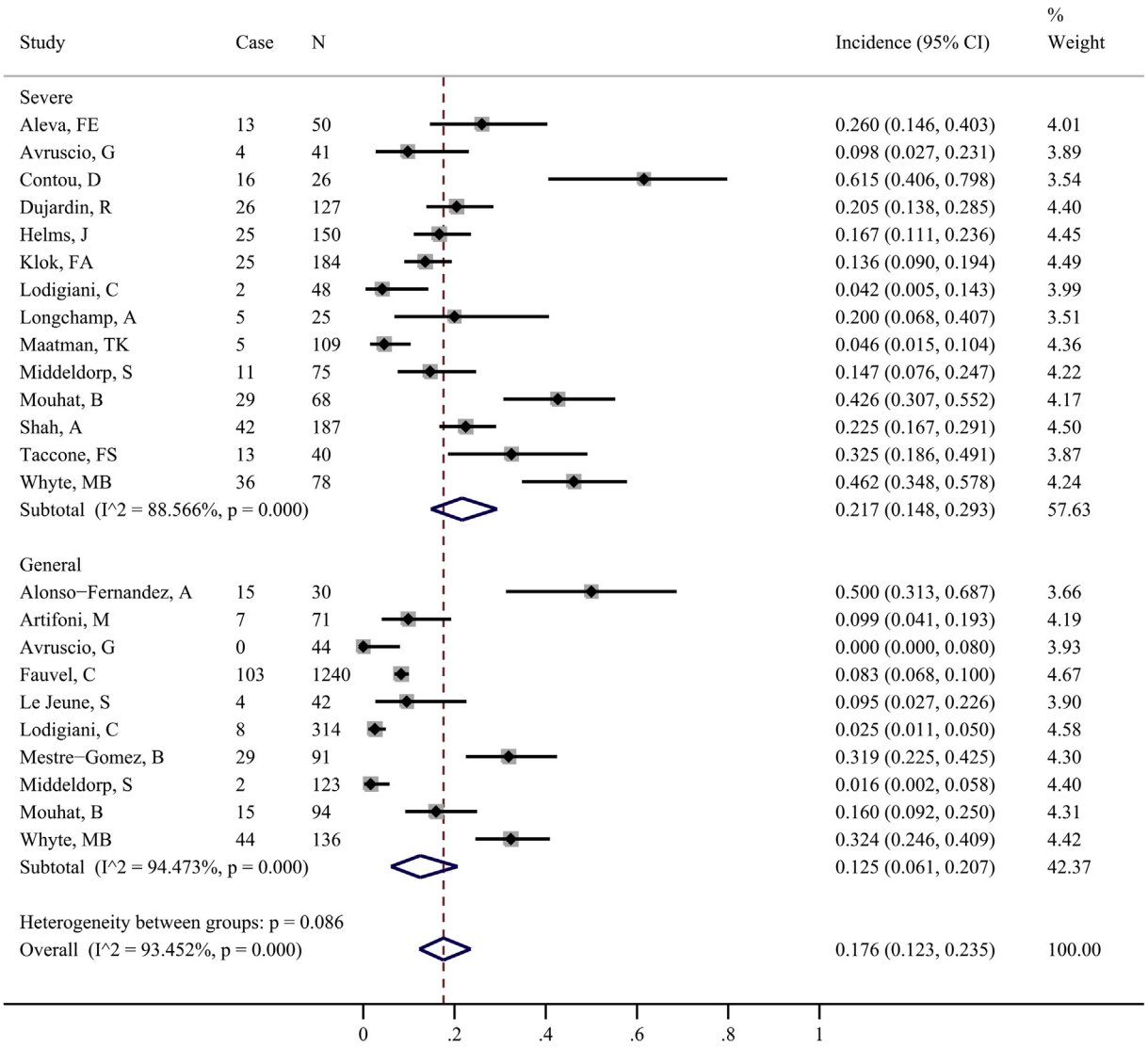

Fig 4. Forest plot representing incidence of pulmonary embolism (PE) among severe and general hospitalized coronavirus disease 2019 (COVID-19) patients. The pooled prevalence rate of PE was 17.6%. The *gray squares* indicate the weights used in the meta-analysis. *Case,* Cases of PE; *CI,* confidence interval; *N,* total number of patients.

analysis (general vs severe subtypes), which likely makes our findings a more accurate reflection of clinical reality.

The incidence of VTE among hospitalized COVID-19 patients in the present meta-analysis seems higher than that among patients without COVID-19. Several meta-analyses have reported that the VTE incidence ranged from 1.25% to 15.7% in patients without COVID-19 undergoing surgery for benign lesions or tumors.[48-50] The overall VTE incidence was 28.3% among the hospitalized COVID-19 patients. Therefore, COVID-19 pneumonia might be an additional risk factor for VTE and should be prevented if possible and treated promptly. However, despite the remarkably high incidence of VTE in the present study, the real-world incidence of VTE among hospitalized COVID-19 patients might have been underestimated. First, the clinical signs and symptoms of PE can be difficult to differentiate from those of COVID-19, especially in patients in ICUs, where their respiratory status is the focus and they will not undergo systematic evaluation for DVT of the lower extremities. Moreover, the strict ICU isolation results in a high threshold for performing the diagnostic tests because of the risk of staff exposure. Third, critically ill patients already receiving full-dose anticoagulation treatment might not require a diagnostic test because the test results would probably not change their clinical care. Therefore, the threshold should be low for screening for DVT or PE in hospitalized COVID-19 patients, especially patients with severe COVID-19.

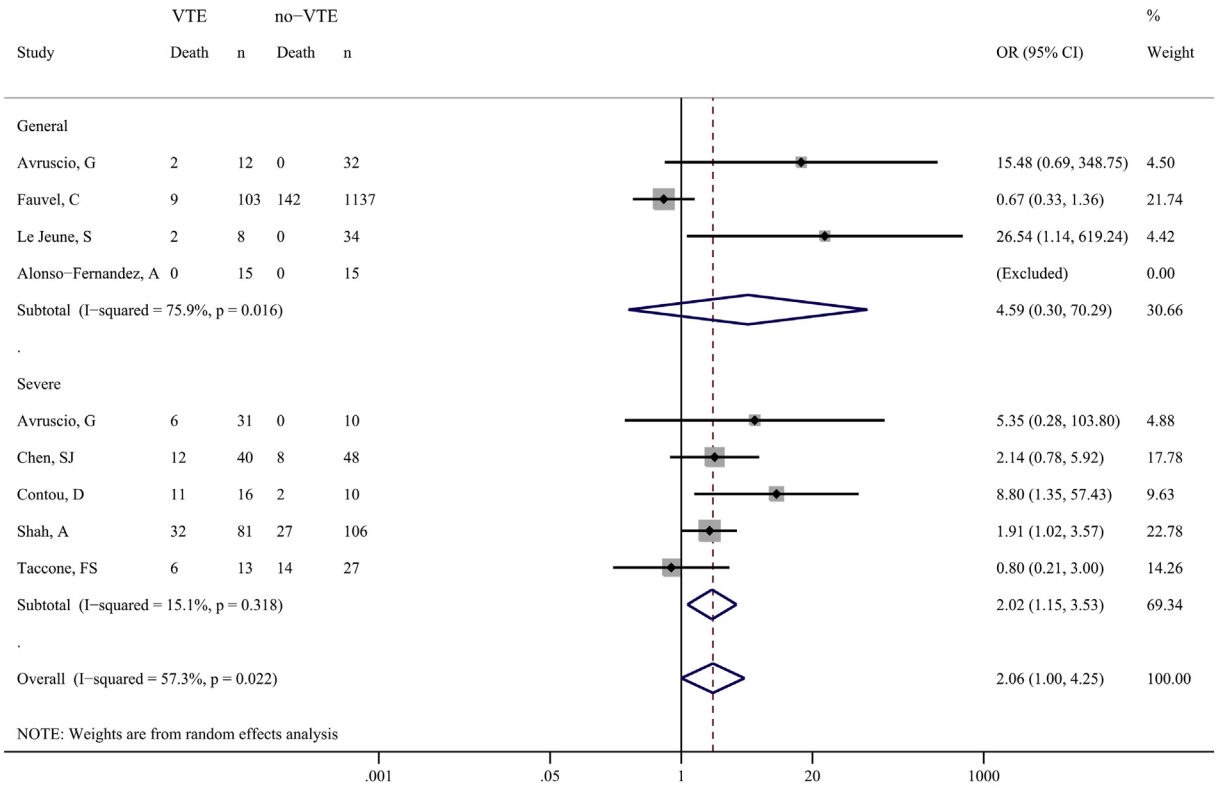

Fig 5. Forest plot representing comparison of mortality between coronavirus disease 2019 patients with and without venous thromboembolism (*VTE*). The *gray squares* indicate the weights used in the meta-analysis. *CI,* Confidence interval; *OR,* odds ratio.

The present review also assessed the effects of VTE on the prognosis of COVID-19 patients. The mortality rate for those with severe COVID-19 and VTE was significantly greater than that of those with severe COVID-19 but without VTE. The weighted mean mortality for the severe COVID-19 patients with VTE was 38.1%. When the severity of COVID-19 was not defined, the mortality between two groups was not significantly different. Zhang et al[36] reported that COVID-19 patients with DVT had a higher death rate than did COVID-19 patients without VTE. In their study, the disease severity was not specified when mortality was compared.[36] However, more patients in the VTE group than in the no-VTE group had been critically ill. The worse prognosis in the VTE group had largely resulted from the dominance of severe COVID-19 patients in VTE group.[36] In the general COVID-19 patients in our meta-analysis, the two groups had similar mortality, which might have resulted from the prompt prophylactic or full-dose anticoagulation therapy provided and the relatively low mortality accompanied by general COVID-19 status.

D-dimer is a laboratory indicator that reputedly predicts for fatal outcomes from PE. In some studies, patients with D-dimers levels of ≥1.0 μg/L had an 18-fold increased mortality risk,[2] and patients who had died of COVID-19 had had higher levels of D-dimer on admission compared with those who had survived.[51] In our review, 13 of the included studies had reported significantly higher D-dimer levels in the COVID-19 patients with VTE than in those without VTE. Therefore, a higher D-dimer level could be an indicator predicting for VTE and a poor prognosis for VTE patients. Moreover, COVID-19 patients who had a combination of a CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≤65 years; a pneumonia severity assessment) score of 3 to 5, a Padua prediction (a VTE risk assessment) score of ≥4, and D-dimer level >1.0 μg/mL had a high risk of VTE.[36] These findings indicate that the clinical suspicion for VTE should be high for COVID-19 patients with high D-dimer levels. Our analysis also found that COVID-19 patients with VTE had significantly lower lymphocyte counts than did patients without VTE in the 2 included studies reporting the lymphocyte count. Thus, an abnormal lymphocyte count could be another marker for VTE in COVID-19 patients. In other studies, COVID-19 patients with DVT had lower lymphocyte counts and longer prothrombin times than did non-DVT patients.[36] Therefore, a combination of high D-dimer levels, low lymphocyte counts, and prolonged prothrombin times probably should prompt high clinical suspicion of VTE in

COVID-19 patients, a consideration that deserves largescale studies. Patients with a high clinical suspicion for VTE according to abnormal laboratory indicators might benefit from prompt diagnostic testing.

The optimal prophylactic scheme for VTE in COVID-19 patients also merits discussion. Dujardin et al[23] showed that despite intermediate-dose prophylaxis, the incidence of VTE has been relatively high. Moreover, some investigators[9,40] have recommended complete-dose thromboprophylaxis, although controlled study evidence is lacking. The bleeding risk of complete-dose anticoagulation should be not ignored. In our analysis, patients who had received only standard-dose prophylaxis had a greater pooled incidence of VTE compared with patients who had received standard prophylaxis combined with another dose (ie, intermediate or complete anticoagulation). Similarly, Jimenez-Guiu et al[42] found that the standard prophylactic anticoagulation group had a higher risk of DVT than did the intermediate or complete anticoagulation group, with no significant differences observed in bleeding complications between the two groups. These results indicate that standard-dose prophylaxis might not be adequate for lowering the incidence of VTE complications in COVID-19 patients. A higher dose of anticoagulation should be attempted for COVID-19 patients, especially those with severe COVID-19 after consideration of the bleeding risks. Ideally, the prophylaxis and therapeutic panel of anticoagulation in COVID-19 patients will be optimized according to evidence from prospective studies comparing the three anticoagulation panels.

Our study had some limitations. First, our meta-analysis included no randomized controlled studies, which seems reasonable, given that, during a pandemic, it is not appropriate to prospectively randomize patients and compare the outcomes. Second, significant statistical heterogeneity existed in the present review (I^2 >50%), which might have resulted from the inconsistency of the inclusion and exclusion criteria used to include patients and the therapeutic panels used across the studies. Third, most of the included studies were retrospective studies, with only six that were prospective. Fourth, we were unable to compare the VTE incidence among the prophylactic, intermediate, and complete anticoagulation groups because the VTE occurrence in these three groups had not been separately reported.

CONCLUSIONS

The overall incidence of VTE among hospitalized COVID-19 patients was 28.3% and was 38% among the hospitalized patients with severe COVID-19. The incidence of PE among hospitalized patients with severe COVID-19 was 21.7%. Severe COVID-19 patients with VTE had a significantly higher mortality rate than did severe COVID-19 patients without VTE. An increased blood D-dimer level might be an indicator of VTE in hospitalized COVID-19 patients. The results of our analysis should be verified in a meta-analysis including more prospective and randomized controlled studies.

AUTHOR CONTRIBUTIONS

Conception and design: LQ
Analysis and interpretation: YL, JC, CW, JJ
Data collection: YL, JC, CW
Writing the article: YL, CW, JJ
Critical revision of the article: JC, LQ
Final approval of the article: YL, JC, CW, JJ, LQ
Statistical analysis: JJ
Obtained funding: JJ, LQ
Overall responsibility: LQ
YL, JC, and CW contributed equally to this article and share co-first authorship.

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Supplementary Table I (online only). Clinical patient characteristics and venous thromboembolism (*VTE*) treatment

Investigator	COVID-19 severity	Patients	VTE		Anticoagulation panel	Anticoagulation drugs
			Hx+	At admission		
Al-Samkari et al[19]	Severe	Hospitalized patients with confirmed COVID-19	NR	No	Mechanical thromboprophylaxis, 2; standard prophylactic anticoagulation, 124; intermediate or complete anticoagulation, 18	Enoxaparin or UFH
	General				Mechanical thromboprophylaxis, 9; standard prophylactic anticoagulation, 231; intermediate or complete anticoagulation, 17	
Aleva et al[37]	Severe	Critically ill hospitalized patients with confirmed COVID-19	NR	No	Standard prophylaxis anticoagulation, 50 (13 developed PE)	LMWH
Alonso-Fernandez et al[38]	General	Hospitalized patients with confirmed COVID-19	1 DVT	3	Standard prophylaxis anticoagulation, 26 (12 developed PE); complete anticoagulation, 3 (3 had PE at admission)	Enoxaparin
Artifoni et al[20]	General	Hospitalized patients with confirmed COVID-19	5	No	Standard prophylactic anticoagulation, 71 (7 developed PE)	Enoxaparin
Avruscio et al[39]	Severe	Hospitalized patients with confirmed COVID-19	1	No	Standard prophylactic anticoagulation, 59; intermediate anticoagulation, 26 (4 developed PE)	Enoxaparin or fondaparinux
	General		1			
Chen et al[21]	Severe	Critically ill hospitalized COVID-19 patients	NR	No	Standard prophylactic anticoagulation, 88	Enoxaparin
Contou et al[22]	Severe	Critically ill hospitalized COVID-19 patients	NR	No	Standard prophylactic anticoagulation, 26 (16 developed PE)	Calcium heparin, sodium heparin, fondaparinux, or enoxaparin
Demelo-Rodriguez et al[40]	General	Hospitalized patients in non-ICU with confirmed COVID-19	0	No	Mechanical thromboprophylaxis, 3; standard prophylactic anticoagulation, 153	Enoxaparin or bemiparin
Dujardin et al[23]	Severe	Hospitalized patients in ICU with confirmed COVID-19	NR	No	Standard prophylactic anticoagulation initially, followed by intermediate anticoagulation, 127 (21 developed PE)	Nadroparin
Fauvel et al[24]	General	Hospitalized patients with confirmed COVID-19	98	No	Standard prophylaxis anticoagulation, 738; intermediate anticoagulation, 99	LMWH or UFH
Helms et al[41]	Severe	Hospitalized patients in ICU with confirmed COVID-19	8	No	Standard prophylactic anticoagulation, 105; complete anticoagulation, 45 (25 developed PE)	LMWH or UFH

Supplementary Table I (online only). Continued.

Investigator	COVID-19 severity	Patients	VTE		Anticoagulation panel	Anticoagulation drugs
			Hx+	At admission		
Jimenez-Guiu et al[42]	General	Hospitalized patients in non-ICU with confirmed COVID-19	0	No	Standard prophylaxis anticoagulation, 37; intermediate anticoagulation, 12; complete anticoagulation, 8	Enoxaparin
Klok et al[9]	Severe	Hospitalized patients in ICU with confirmed COVID-19	NR	No	Standard prophylaxis or intermediate anticoagulation, 184 (25 developed PE)	Nadroparin
Le Jeune et al[25]	General	Hospitalized patients in non-ICU with confirmed COVID-19	NR	No	Standard prophylaxis anticoagulation, 25; intermediate anticoagulation, 10; complete anticoagulation, 7 (4 developed PE)	NR
Lodigiani et al[26]	Severe	Hospitalized patients with confirmed COVID-19	0	No	Standard prophylaxis anticoagulation, 17; complete anticoagulation, 2 (2 developed PE)	LMWH
	General		12		Standard prophylaxis anticoagulation, 133; intermediate anticoagulation, 67; complete anticoagulation, 74 (8 developed PE)	
Longchamp et al[27]	Severe	Hospitalized patients in ICU with confirmed COVID-19	0	No	Standard prophylactic anticoagulation from admission, 25; complete anticoagulation after thromboembolic event 8 (5 developed PE)	Heparin or enoxaparin
Longhitano et al[43]	Severe or general	Hospitalized patients with confirmed COVID-19	0	No	Standard prophylaxis anticoagulation, 27; intermediate anticoagulation, 23; complete anticoagulation, 24 (9 developed PE)	Enoxaparin or heparin
Maatman et al[28]	Severe	Hospitalized patients in ICU with confirmed COVID-19	NR	2	Standard prophylactic anticoagulation, 109 (5 developed PE)	Enoxaparin or heparin
Mestre-Gomez et al[29]	General	Hospitalized patients with confirmed COVID-19	2 PE and 1 DVT	No	Standard prophylactic anticoagulation (29 developed PE)	LMWH
Middeldorp et al[30]	Severe	Hospitalized patients with confirmed COVID-19	2	No	Intermediate anticoagulation, 75 (11 developed PE)	Nadroparin
	General		9		Standard prophylactic anticoagulation, 123 (2 developed PE)	

(Continued on next page)

Supplementary Table I (online only). Continued.

Investigator	COVID-19 severity	Patients	VTE		Anticoagulation panel	Anticoagulation drugs
			Hx+	At admission		
Mouhat et al[31]	Severe or general	Hospitalized patients with confirmed COVID-19	13	9	Standard prophylactic anticoagulation or complete anticoagulation, 141 (44 developed PE)	Enoxaparin, UFH, or oral anticoagulation
Shah et al[32]	Severe	Hospitalized patients in ICU with confirmed COVID-19	7	No	Standard prophylactic anticoagulation, 187 (42 developed PE)	LWMH
Taccone et al[33]	Severe	Hospitalized patients in ICU with confirmed COVID-19	0	No	Standard prophylactic anticoagulation, 22 (11 developed PE); complete anticoagulation, 18 (2 developed PE)	Enoxaparin or UFH
Trigonis et al[34]	Severe	Critically ill hospitalized patients with confirmed COVID-19	NR	No	Different anticoagulation (unspecified)	LMWH or UFH
Whyte et al[35]	Severe or general	Hospitalized patients with confirmed COVID-19	21	No	Standard prophylaxis, complete, or no anticoagulation, 214 (80 developed PE)	Enoxaparin or UFH
Zhang et al[36]	Severe or general	Hospitalized patients with confirmed COVID-19	1	No	Standard prophylactic anticoagulation, 53; no anticoagulation, 90	LMWH

COVID-19, Coronavirus disease 2019; *DVT*, deep vein thrombosis; *Hx+*, positive history; *ICU*, intensive care unit; *LMWH*, low-molecular-weight heparin; *PE*, pulmonary embolism; *UFH*, unfractionated heparin.

Supplementary Table II (online only). Incidence of venous thromboembolism (*VTE*) among patients administered standard prophylactic anticoagulation alone or mixed anticoagulation

	Incidence (95% CI)		
Anticoagulation	**VTE**	**DVT**	**PE**
Standard prophylaxis alone	32.7 (21.4-45.2)	21.3 (10.1-35.2)	18.6 (7.7-32.8)
Mixed anticoagulation[a]	26.1 (18.6-34.3)	16.1 (7.2-27.4)	17.3 (11.2-24.2)
P value	.367	.541	.854

CI, Confidence interval; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism.
[a]Defined as standard prophylaxis anticoagulation and intermediate anticoagulation, standard prophylaxis anticoagulation and complete anticoagulation, or a combination of the three panels.

Supplementary Table III (online only). Laboratory indicators of coronavirus disease 2019 (COVID) patients with and without venous thromboembolism (*VTE*)

Investigator	Group	Patients, No.	Age,[a] years	D-dimer,[a] μg/mL	Lymphocyte count,[a] 10^9/L	Fibrinogen,[a] g/L	Prothrombin time, seconds
Alonso-Fernandez et al[38]	PE	15	67 (63-73)	2.6 (1.8-7.1)	1.0 (0.7-1.5)	6.16 (3.90-8.24)	12.7 (12.1-15.0)
	No PE	15	57 (48-69)[b]	1.6 (0.6-3.5)	1.6 (1.0-2.0)	5.23 (4.01-7.33)	10.3 (12.6-14.9)
Artifoni et al[20]	VTE	16	61 (40.8-79)	1.63 (0.86-4.94)	0.92 (0.75-1.25)	5.2 (4.6-6.6)	NR
	No VTE	55	64 (47.5-75)	0.67 (0.45-1.12)[b]	0.99 (0.72-1.29)	4.8 (4.3-6.6)	NR
Avruscio et al[39]	VTE	43	NR	1.31 (0.58-2.49)	NR	4.9 (3.9-5.7)	NR
	No VTE	42	NR	0.26 (0.15-0.93)	NR	5.0 (3.5-5.6)	NR
Chen et al[21]	DVT	40	63 (56-70)	6.41 (2.75-10.94)	0.75 (0.60-1.04)	NR	12.9 (12.6-13.6)
	No DVT	48	64 (55-73)	3.10 (1.39-7.60)[b]	0.84 (0.53-1.20)	NR	13.2 (12.7-14.1)
Contou et al[22]	PE	16	63 (47-77)	5.3 (1.8-20)	NR	7.8 (3.2-11.7)	NR
	No PE	10	63 (46-73)	1.9 (0.5-19)	NR	7.8 (4.1-9)	NR
Demelo-Rodriguez et al[40]	DVT	23	66.7 ± 15.2	4.53 (1.93-9.14)	1.0 (0.6-1.3)	NR	NR
	No DVT	133	68.4 ± 14.4	2.05 (1.43-3.54)[b]	0.9 (0.6-1.3)	NR	NR
Dujardin et al[23]	VTE	53	62 (55-71)	2.31 (0.82-29.2)	NR	7.5 (5.6-8.6)	11.3 (10.8-11.9)
	No VTE	74	62 (55-70)	1.25 (0.73-3.00)	NR	7.7 (5.6-8.3)	11.3 (10.7-12.0)
Fauvel et al[24]	PE	103	63 ± 16	3.52 ± 4.39	1.3 ± 1.2	6.3 ± 2.0	NR
	No PE	1137	64 ± 17	1.37 ± 4.12[b]	1.3 ± 3.4	6.1 ± 1.6	NR
Jimenez-Guiu et al[42]	DVT	6	NR	0.58 ± 0.57	NR	NR	NR
	No DVT	51	NR	0.47 ± 0.19	NR	NR	NR
Le Jeune et al[25]	DVT	8	77.7 ± 15.2	1.99 (1.37-6.45)	0.80 (0.53-1.00)	6.06 (5.10-6.49)	NR

Supplementary Table III (online only). Continued.

Investigator	Group	Patients, No.	Age,[a] years	D-dimer,[a] μg/mL	Lymphocyte count,[a] 10^9/L	Fibrinogen,[a] g/L	Prothrombin time, seconds
	No DVT	34	61.5 ± 19.0[b]	1.25 (0.87-3.43)	0.89 (0.70-1.01)	5.60 (4.82-6.76)	NR
Longhitano et al[43]	VTE	21	66.7 ± 16.8	2.79 (1.42-5.73)	0.74 ± 0.14	6.45 (4.22-7.96)	15.3 ± 2.6
	No VTE	53	69.4 ± 14.5	1.08 (0.45-1.59)[b]	0.82 ± 0.29	5.05 (4.13-6.34)	14.3 ± 2.6
Maatman et al[28]	VTE	31	60 ± 17	0.90 (0.43-3.57)	NR	5.28 (4.35-6.32)	NR
	No VTE	78	62 ± 15	0.46 (0.28-0.76)[b]	NR	5.35 (4.25-6.81)	NR
Mestre-Gomez et al[29]	PE	29	65 (56-73)	1.45 (0.55-3.32)	NR	1.81 (1.60-3.21)	12.5 (11.9-13.5)
	No PE	62	64.5 (57-75)	0.72 (0.21-1.64)[b]	NR	2.70 (2.06-4.32)	12.45 (11.8-13.3)
Middeldorp et al[30]	VTE	39	62 ± 10	2.6 (1.1-18)	0.59 (0.47-0.83)	NR	NR
	No VTE	159	60 ± 15	1.0 (0.7-1.7)	1.00 (0.80-1.30)	NR	NR
Mouhat et al[31]	PE	44	66.5 ± 11.4	5.36 (2.93-12.28)	0.94 ± 0.42	NR	NR
	No PE	118	65.2 ± 13.6	1.31 (0.80-2.34)[b]	1.28 ± 0.38[b]	NR	NR
Shah et al[32]	VTE	81	59 (53-66)	6.14 (1.64-10.00)	0.80 (0.50-1.10)	6.9 (6.0-9.6)	12.0 (11.0-13.3)
	No VTE	106	56 (48-63)	1.26 (0.79-5.54)[b]	0.80 (0.56-1.10)	7.4 (6.0-10.0)	12.8 (11.0-14.36)
Taccone et al[33]	PE	13	58 (53-61)	8.28 (5.98-11.48)	0.86 (0.55-1.68)	NR	NR
	No PE	27	63 (58-68)	2.30 (1.33-5.75)[b]	0.99 (0.80-1.27)	NR	NR
Trigonis et al[34]	DVT	19	64.1 ± 14.0	5.61 (2.94-11.87)	NR	NR	NR
	No DVT	26	58.3 ± 15.4	2.27 (1.08-3.43)[b]	NR	NR	NR
Whyte et al[35]	PE	80	63.5 ± 13.4	8.00 (4.34-8.00)	NR	NR	NR
	No PE	134	59.6 ± 16.2	2.06 (1.21-4.41)[b]	NR	NR	NR
Zhang et al[36]	DVT	66	67 ± 12	6.6 (2.5-8.0)	0.68 (0.49-1.14)	NR	14.2 (13.3-15.4)
	No DVT	77	59 ± 16[b]	0.9 (0.4-3.5)[b]	0.98 (0.68-1.37)[b]	NR	12.9 (12.3-14.0)[b]

DVT, deep vein thrombosis; *NR*, not reported; *PE*, pulmonary embolism.
[a]Data presented as median (interquartile range) or mean ± standard deviation.
[b]VTE vs no VTE, $P < .05$.