COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies

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Abstract

Coronavirus disease 2019 (COVID-19) may have a wide spectrum of clinical presentations, leading in some cases to a critical condition with poor long-term outcomes and residual disability requiring post-acute rehabilitation. A major concern in severe COVID-19 is represented by a concomitant prothrombotic state. However, contrasting data are available about the prevalence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). A detailed search on the association of COVID-19 with thromboembolic complications was conducted in the main electronic databases (PubMed, Web of Science, and Scopus) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The weighted mean prevalence (WMP) with 95% confidence interval (95% CI) was calculated with the random-effects model. Twenty studies enrolling 1,988 COVID-19 patients were included. The WMP of VTE was 31.3% (95% CI: 24.3–39.2%). The WMP of DVT was 19.8% (95% CI: 10.5–34.0%), whereas the WMP of PE was 18.9% (95% CI: 14.4–24.3%). Similar results were obtained when specifically analyzing studies on patients admitted to intensive care units and those on patients under antithrombotic prophylaxis. Regression models showed that an increasing age was associated with a higher prevalence of VTE (Z-score: 3.11, $p = 0.001$), DVT (Z-score: 2.33, $p = 0.002$), and PE (Z-score: 3.03, $p = 0.002$), while an increasing body mass index was associated with an increasing prevalence of PE (Z-score $= 2.01$, $p = 0.04$). Male sex did not impact the evaluated outcomes. The rate of thromboembolic complications in COVID-19 patients is definitely high. Considering the risk of fatal and disabling complications, adequate screening procedures and antithrombotic strategies should be implemented.

Keywords
► SARS-CoV-2
► COVID-19
► thrombosis
► disability
► anticoagulants.

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China.[1] Despite the attempts to minimize exportation, SARS-CoV-2 showed an international spread, thus becoming a public health emergency.[2] Therefore, in March 2020, the World Health Organization (WHO) declared the novel coronavirus outbreak pandemic.[3]

The rapidly increasing number of studies on SARS-CoV-2 infection indicates that this viral agent can cause coronavirus disease 2019 (COVID-19), a syndrome with a wide spectrum

of clinical presentations.[4,5] COVID-19 may range from a mild disease with flulike symptoms to a critical care respiratory condition requiring specialized management at intensive care units (ICUs),[6–8] with poor long-term outcomes and residual chronic disability.[9,10]

Besides the respiratory manifestations with severe disabling complications, another major concern is represented by evidence of consistent hemostatic changes in patients with severe or critical COVID-19, likely related to a prothrombotic switch.[11,12]

Among COVID-19 patients, it is reasonable to assume that those with a very severe disease could exhibit high risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Critically ill patients with COVID-19 are bedridden in ICU because of acute infective disease determining respiratory failure, thus resulting in a high VTE risk, as predicted by a Padua score (bedridden: 3 points; infection: 1 point; respiratory failure: 1 point).[13] Contrasting data are currently available about the prevalence of thromboembolic events in COVID-19 patients.

The aim of the present study was to perform a systematic literature search with meta-analysis of studies reporting the prevalence of VTE, DVT, or PE in patients with COVID-19. Moreover, we implemented some meta-regression models to evaluate the effect of demographic and clinical variables on the evaluated outcomes.

Materials and Methods

We developed a protocol for this systematic review, defining the search strategy, the outcomes, the inclusion and exclusion criteria, the approach for quality assessment, and the statistical methods.

Search Strategy and Selection Criteria

To detect all available studies on the association of COVID-19 with thromboembolic complications, we conducted a systematic literature search in PubMed, Web of Science, and Scopus according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The last search was performed on May 19, 2020, with no language restriction, by using the following terms in all possible combinations: *COVID-19, SARS-CoV-2, VTE, DVT, PE, vein, venous, thrombosis, thrombosis thrombotic, thromboembolism, pulmonary, embolism, embolic*, and *occlusion*. Moreover, the lists of the bibliographic references of all included articles were manually screened. In case of missing data among studies fulfilling the inclusion criteria, the authors were contacted by e-mail to try to claim the original data. Two authors (A.D.M. and P.A.) analyzed each article and separately performed the extraction of data. In case of disagreement, a third investigator was consulted (M.N.D.D.M.). Discrepancies were resolved by consensus. Overall, selection results showed a high inter-reader agreement ($\kappa = 1.00$) and were reported according to PRISMA flow-chart (►**Fig. 1**).

According to a predetermined protocol, all studies reporting data about the association of COVID-19 with thromboembolic complications were included. Reviews and articles on animal models were excluded. Overall, we included in the analysis all studies providing data about the prevalence of VTE, DVT, or PE among COVID-19 patients, with VTE being defined as the presence of any thromboembolic complication (DVT, PE, or a combination of both).[15] Studies reporting on the autopsy evidence of thromboembolic events were also included. Superficial vein thrombosis was not considered as VTE episode and was excluded from the analysis. In each study, data regarding sample size, mean age of enrolled patients, percentage of male patients, and body mass index (BMI) were extracted. Formal quality score adjudication was not used since most included studies were small cohort studies.

Data Synthesis and Statistics

Data synthesis and analyses were performed by using comprehensive meta-analysis (version 2; Biostat). The prevalence of VTE, DVT, and of PE was expressed as weighted mean prevalence (WMP) with 95% confidence intervals (95% CIs). The pooled effect was tested by means of Z-scores, with $p < 0.05$ being considered statically significant. We evaluated statistical heterogeneity among studies with chi-squared Cochran's Q-test and with I^2 index, which measures the inconsistency among results of studies and defines the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. In particular, an I^2 value of 25% corresponds to low, 25 to 50% to moderate, and 50% to high heterogeneity.[16] Funnel plots of the logit event rate versus the standard error were used as a graphical representation of publication bias. To detect a potential small-study effect, funnel plots were visually inspected for asymmetry. Moreover, the Egger test was used to assess publication bias over and above any subjective evaluation, with $p < 0.10$ being considered statistically significant.[17] To be as conservative as possible, the random-effects method was used to take into account the variability among included studies.

Subgroup Analyses

We performed separate subgroup analyses on (1) studies specifically including ICU patients; (2) studies specifically including patients receiving antithrombotic prophylaxis; and (3) studies systematically performing VTE screening.

Meta-regression Analyses

We hypothesized that mean age of the study population, the percentage of males, and BMI may affect the rate of thromboembolic complications observed in different studies. Thus, we planned to perform meta-regression analyses after implementing regression models with the prevalence of VTE, DVT, and PE as dependent variables (y) and the aforementioned covariates as independent variables (x). Comprehensive meta-analysis software (version 2, Biostat) was used for the multivariate approach.

Results

After excluding duplicates, the search detected 222 articles. Of these, 140 were excluded because they were off the topic (after scanning the title and/or the abstract), and another 40
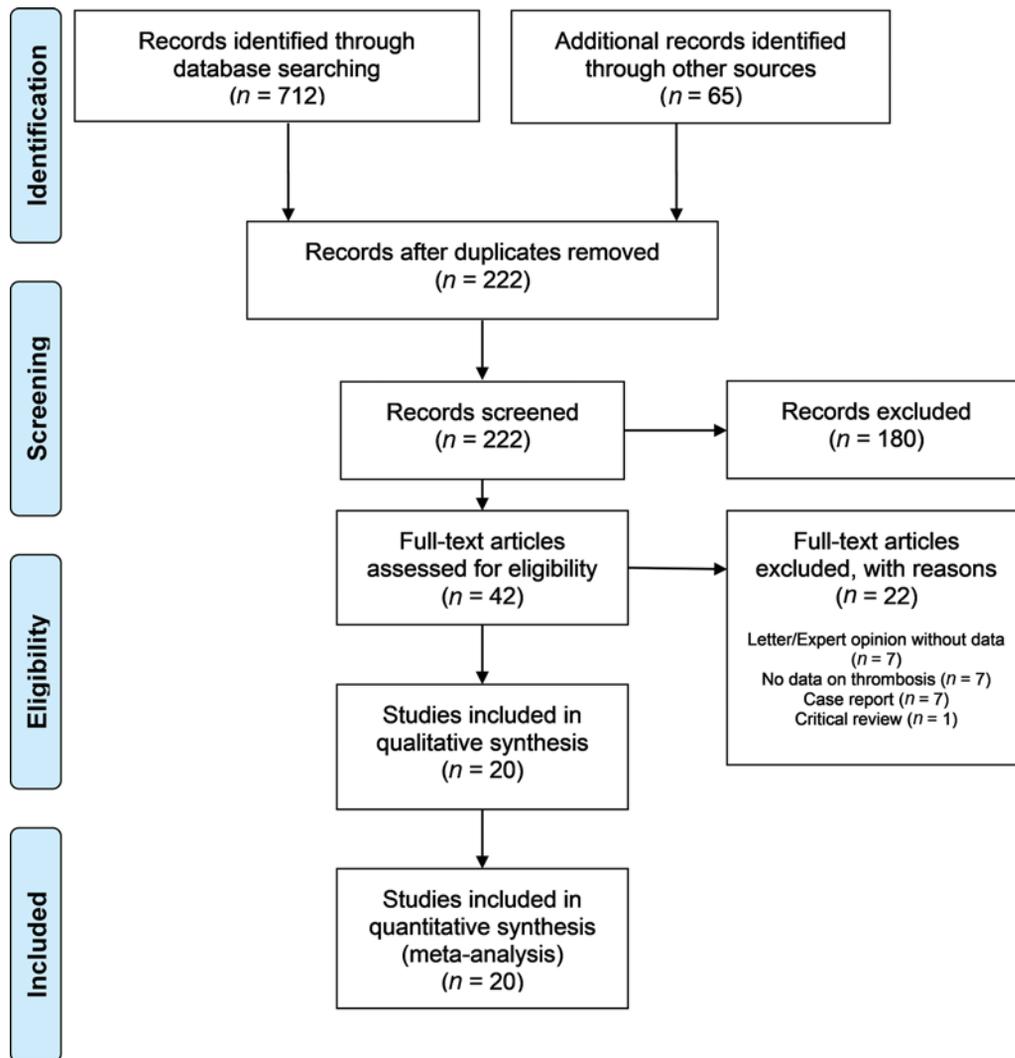
Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

because they were reviews/commentaries or lacked of data of interest. Another 22 studies were excluded after full-length paper evaluation (►**Fig. 1**). Studies by Lodigiani et al[18] and Middeldorp et al[19] provided separate data for ICU patients and general ward patients. The two populations were analyzed as separate datasets.

A total of 20 studies (22 datasets)[18–37] enrolling 1,988 COVID-19 patients were finally included in the meta-analysis.

Study Characteristics

Major characteristics of included studies are shown in ►**Table 1**. The number of patients varied from 11 to 328, with mean age of 64.3 years (from 51.7 to 80.5 years). Eleven studies[18,19,21,24,25,28,30,32–34,36] specifically enrolled patients admitted to ICU. A total of 66.8% of patients were males (range: 45.7–90.9%) and the mean BMI was 28.2 kg/m^2 (range: 23.6–31.3 kg/m^2). Antithrombotic prophylaxis was used by 78.4% of patients (range: 0–100%).

Prevalence of Thromboembolic Complications

The WMP of VTE in the 1,988 COVID-19 patients was 31.3% (95% CI: 24.3–39.2%, ►**Fig. 2**).[18–37] The heterogeneity among

studies was significant (I^2: 89.2%, $p < 0.001$) and was not reduced by the exclusion of one study at time. Results were similar when specifically analyzing studies on ICU patients (WMP: 32.7%, 95% CI: 21.9–45.7%; I^2: 89.9%, $p < 0.001$).[18,19,21,24,25,28,30,32–34,36] When analyzing studies specifically enrolling patients receiving antithrombotic prophylaxis, the WMP of VTE was 23.9% (95% CI: 15.9–34.4%; I^2: 87.8%, $p < 0.001$).[18–20,24,25,28,30,33,34] The WMP of VTE was 37.1% (95% CI: 19.0–59.8%) for studies systematically performing thrombosis screening in all enrolled patients, and 29.4% (95% CI: 22.5–37.4%) for those performing imaging tests in symptomatic patients (►**Table 2**).

Twelve studies (13 datasets)[19,21,22,24,25,28–30,32,33,35,37] showed that the WMP of DVT among 1,157 COVID-19 patients was 19.8% (95% CI: 10.5–34.0%; I^2: 93.3%, $p < 0.001$) (►**Fig. 2**). Similar results were obtained specifically analyzing studies on ICU patients (WMP: 17.9%, 95% CI: 6.6–40.5%; I^2: 94.0%, $p = 0.346$). A lower rate of DVT was found when considering studies on patients receiving antithrombotic prophylaxis (WMP: 8.0%, 95% CI: 2.3–2.4%; I^2: 92.7%, $p < 0.001$). A higher WMP of DVT was found in studies systematically screening all enrolled patients (►**Table 2**).

Table 1 Characteristics of included studies

Study	Patients (n)	Age (y)	Males (%)	BMI (kg/m²)	ICU patient (%)	Anticoagulation (%)
Bompard et al, 2020[20]	135	64.7	70.0	–	18.0	100
Cui et al, 2020[21]	81	59.9	45.7	–	100	0
Demelo-Rodríguez et al, 2020[22]	156	68.1	65.4	26.9	11.5	98.0
Grillet et al, 2020[23]	100	66.0	70.0	–	39.0	–
Helms et al, 2020[24]	150	62.3	81.3	–	100	100
Klok et al, 2020[25]	184	64.0	76.0	–	100	100
Lax et al, 2020[26]	11	80.5	72.7	–	–	91.0
Leonard-Lorant et al, 2020[27]	106	64.0	66.0	27.0	45.2	39.6
Llitjos et al, 2020[28]	26	68.0	77.0	30.0	100	100
Lodigiani et al, 2020a[18]	18	–	–	–	100	100
Lodigiani et al, 2020b[18]	26	–	–	–	0	–
Marone and Rinaldi, 2020[29]	30	–	–	–	0	–
Middeldorp et al, 2020a[19]	75	62.0	77.0	27.0	100	100
Middeldorp et al, 2020b[19]	123	60.0	59.0	28.0	0	100
Poissy et al, 2020[30]	107	57.0	59.1	29.0	100	100
Poyiadi et al, 2020[31]	328	61.3	45.9	–	25.3	37.2
Ren et al, 2020[32]	48	70.7	54.2	–	100	98
Spiezia et al, 2020[33]	22	67.0	90.9	30.0	100	100
Thomas et al, 2020[34]	63	59.0	69.0	–	100	100
Wichmann et al, 2020[35]	12	73.0	75.0	28.7	41.7	33.3
Wright et al, 2020[36]	44	51.7	63.6	31.3	100	54.5
Zhang et al, 2020[37]	143	63.0	51.7	23.6	10.5	37.1

Abbreviations: BMI, body mass index; ICU, intensive care unit; n, number; y, years.
^aNumber of patients evaluated with ultrasound imaging. Total numbers of enrolled patients were 48 ICU patients and 314 general ward patients.

Fourteen studies (16 datasets)[18–20,23–25,27,28,30,31,34,35,37] showed that the WMP of PE among 1,593 COVID-19 patients was 18.9% (95% CI: 14.4–24.3%; I^2: 76.3%, $p < 0.001$) (►**Fig. 2**). Similar results were obtained specifically analyzing studies on ICU patients (WMP: 16.1%, 95% CI: 13.1–19.6%; I^2: 13.0%, $p = 0.330$)[18,19,24,25,28,30,34] and studies on patients receiving antithrombotic prophylaxis (WMP: 15.4%, 95% CI: 11.2–20.8%; I^2: 66.6%, $p = 0.002$).[18–20,24,25,28,30,34] Moreover, no difference in PE rate was observed between studies systematically performing thrombosis screening in all enrolled patients and those performing imaging tests in symptomatic patients (►**Table 2**).

Publication Bias
Funnel plot examination (►**Fig. 3**) suggested the absence of publication bias and of small-study effect, confirmed by the Egger test for studies reporting on the prevalence of VTE ($p = 0.621$), DVT ($p = 0.136$), and PE ($p = 0.314$) in COVID-19 patients.

Meta-regression Analyses
Regression models (►**Fig. 4**) showed that an increasing age was associated with a higher prevalence of VTE (Z-score: 3.11, $p = 0.001$), DVT (Z-score: 2.33, $p = 0.002$), and PE (Z-

score: 3.03, $p = 0.002$) in COVID-19 patients. In addition, an increasing BMI was associated with an increasing prevalence of PE (Z-score: 2.01, $p = 0.04$), but not of VTE (Z-score: −0.20, $p = 0.843$) or DVT (Z-score: −0.65, $p = 0.517$). The rate of VTE, DVT, or PE in COVID-19 patients was not impacted by the prevalence of male sex (Z-score: 0.009, $p = 0.999$; Z-score: −0.99, $p = 0.321$; and Z-score: 1.03, $p = 0.304$, respectively).

Discussion

Results of the present meta-analysis consistently show that COVID-19 can be associated with thromboembolic complications. In particular, we found that the prevalence of VTE is ≈30% in COVID-19 patients, with DVT being reported for ≈20% and with PE being reported for ≈18% of patients. Regression models showed that an increasing age is associated with a higher prevalence of VTE, DVT, or PE, while an increasing BMI is associated with an increasing prevalence of PE. No impact of male sex on the evaluated outcomes was found.

To the best of our knowledge, this is the first meta-analysis summarizing the growing amount of literature data on the prevalence of thromboembolic events in patients with COVID-19, a respiratory transmitted virus that in 6 months afflicted more than 7 million people and killed more than 400,000

Venous Thromboembolism
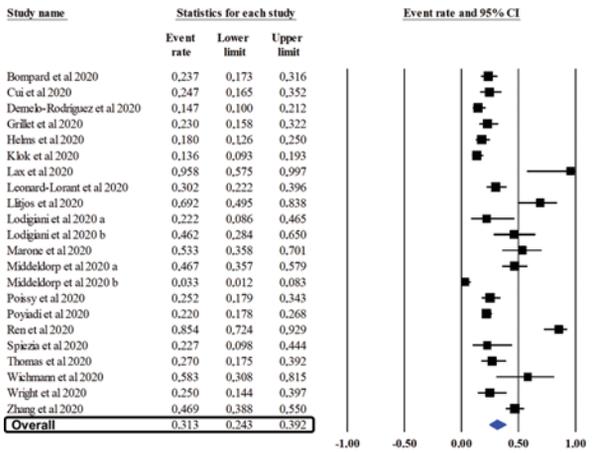
Deep Vein Thrombosis
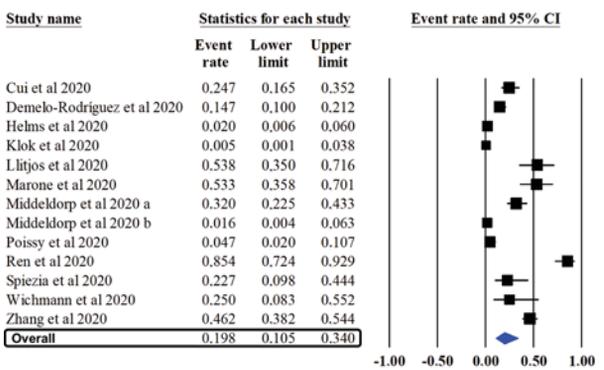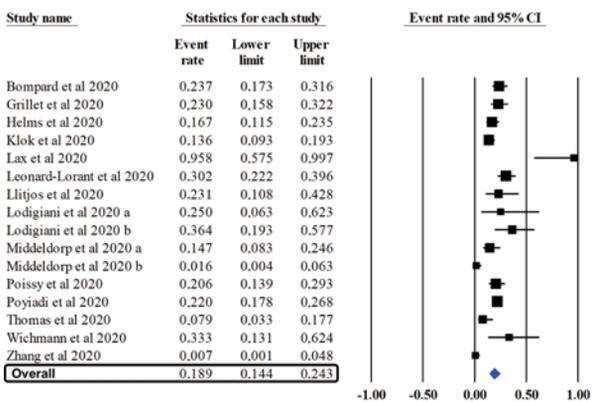

Pulmonary Embolism

Fig. 2 Prevalence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism in COVID-19 patients.

people worldwide. Besides the respiratory syndrome with severe disabling complications, the hypercoagulable state in COVID-19 patients may lead to a high thrombotic risk with dramatic impact on prognosis and mortality.[35]

It is plausible that the severity of COVID-19 infection could be an important determinant in the onset of VTE as critically ill patients are bedridden in ICU due to an acute infective disease determining respiratory failure, with a Padua prediction score always >5.[13] In keeping with this, it should be considered that obesity and an older age, which may further increase the VTE risk and the final Padua score, are potential risk factors for

Table 2 Subgroup analyses

	No. of studies	No. of patients	Effect size WMP [95% CI]
VTE			**Panel A**
No screening	15 (17 datasets)	1,460	WMP: 29.4% [22.5%, 37.4%] $I^2 = 85.3\%$; $p < 0.0001$
Screening	5 (5 datasets)	528	WMP: 37.1% [19.0%, 59.8%] $I^2 = 94.8\%$; $p < 0.0001$
DVT			**Panel B**
No screening	8 (9 datasets)	729	WMP: 12.1% [4.5%, 28.7%] $I^2 = 97.9\%$; $p < 0.0001$
Screening	4 (4 datasets)	428	WMP: 41.3% [18.1%, 69.2%] $I^2 = 70.7\%$; $p < 0.0001$
PE			**Panel C**
No screening	12 (14 datasets)	1,350	WMP: 20.5% [18.3%, 22.9%] $I^2 = 74.0\%$; $p < 0.0001$
Screening	2 (2 datasets)	243	WMP: 19.7% [13.5%, 27.8%] $I^2 = 92.4\%$; $p < 0.0001$

Abbreviations: 95% CI, 95% confidence interval; WMP, weighted mean prevalence.
Note: Venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) from studies with and without systematic screening of thrombotic episodes.

severe COVID-19.[5] Accordingly, our regression models showed that an increasing age and BMI were associated with an increased prevalence of thromboembolic events.

However, the relationship between SARS-CoV-2 infection and the hemostatic imbalance of COVID-19 patients seems to be more complex and not fully explained by the presence of traditional VTE risk factors. In keeping with this, Clayton et al reported a 4% incidence of VTE in patients with pneumonia secondary to respiratory tract infections.[38] Our results show that, compared with this evidence, the rate of VTE in COVID-19 patients is ≈7- to 8-fold higher as compared with other respiratory infections. Accordingly, based on previous meta-analytical data,[39] the frequency of thromboembolic complications in ICU patients is ≈12%. Thus, an indirect comparison with results of our subgroup analysis on ICU suggests that the probability of VTE is higher in severe COVID-19 as compared with the general ICU patient.

In our meta-analysis, the fact that most included studies reported ongoing thromboprophylaxis at the time of VTE by using standard or even therapeutic doses of heparin further supports the hypothesis that SARS-CoV-2 itself may be an additional thrombotic stimulus, over and above traditional VTE risk factors. Accordingly, in the frame of subgroup
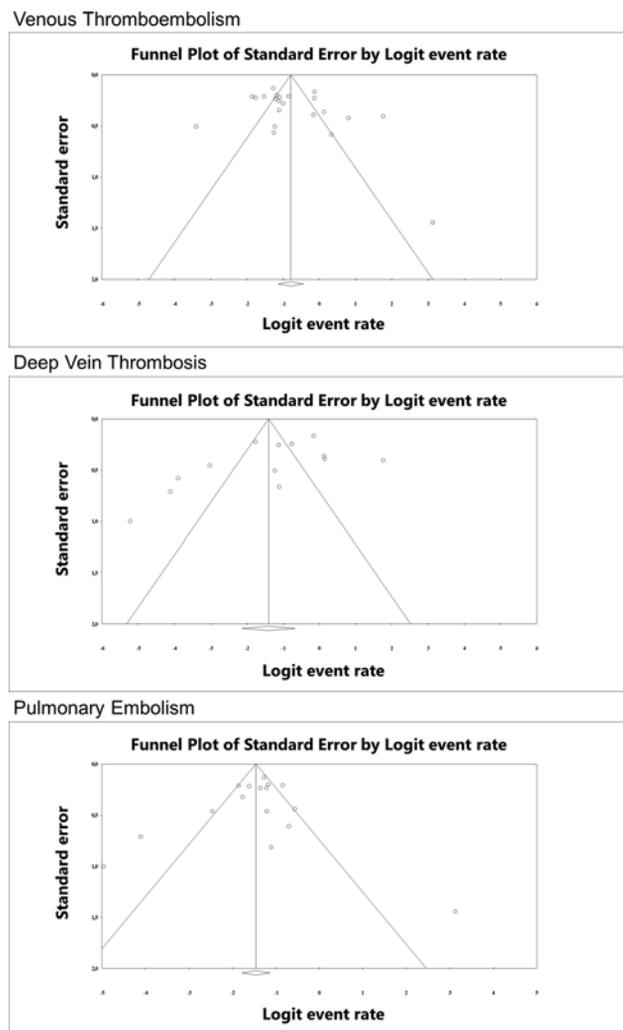
Venous Thromboembolism

Funnel Plot of Standard Error by Logit event rate

Venous Thromboembolism

Regression of Age on Logit event rate

Deep Vein Thrombosis

Funnel Plot of Standard Error by Logit event rate

Deep Vein Thrombosis

Regression of Age on Logit event rate

Pulmonary Embolism

Funnel Plot of Standard Error by Logit event rate

Pulmonary Embolism

Regression of Age on Logit event rate

Fig. 3 Funnel plot of standard error by event rate of studies reporting on the prevalence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism in COVID-19 patients.
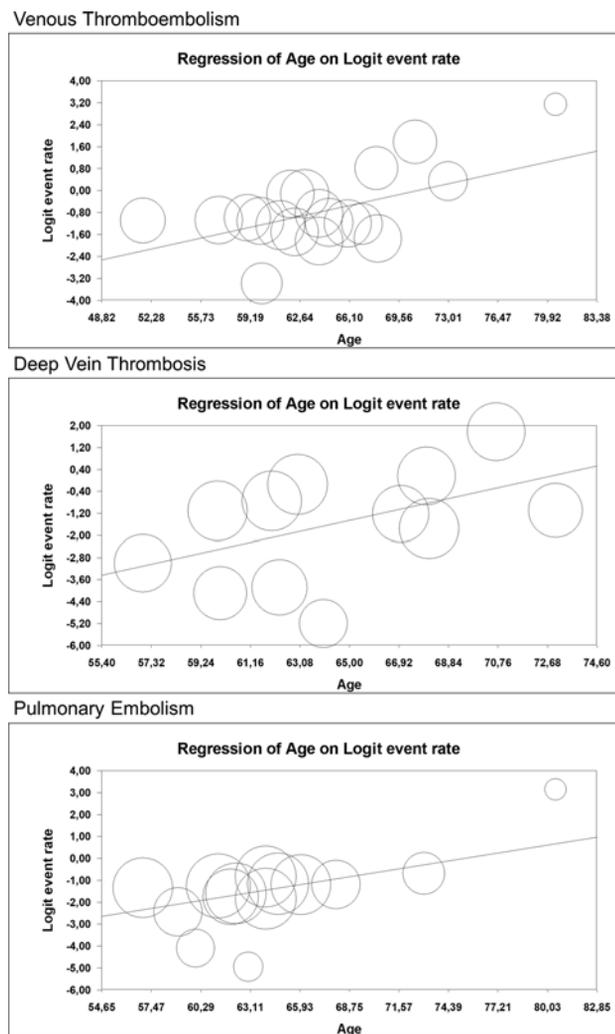
Fig. 4 Metaregression analysis. Impact of age on the prevalence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism in COVID-19 patients.

analyses, we confirmed a high prevalence of VTE ($\approx$24%), DVT ($\approx$10%), and PE ($\approx$15%) also when analyzing studies on patients receiving antithrombotic prophylaxis.

The thrombogenicity of COVID-19 has led some authors to wonder whether such an exceptionally high prevalence of thrombotic complications should be interpreted as a consequence of a localized thrombotic process in the lungs rather than an embolic phenomenon.[40] In detail, it has been hypothesized that the inflammatory reaction in the lungs causes endothelial dysfunction, thus leading to the formation of pulmonary microthrombi.[40] In keeping with this, the histological analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis and microangiopathy, with alveolar capillary microthrombi being ninefold more prevalent in COVID-19 patients than in patients with H1N1 influenza.[41] This may have relevant implications as the composition of pulmonary emboli and pulmonary microthrombi is different. In fact, while emboli reflect the composition of the distal part of the venous thrombi from which they originate, pulmonary microthrombi contain a large amount of platelets and fibrin.[42] It is reasonable to assume

that such different composition may significantly impact both therapeutic and prophylactic strategies.[40]

Taken together, the currently available data may suggest that SARS-CoV-2 infection can rapidly evolve into a severe condition with pulmonary and multiorgan involvement, potentially resulting in a consistent hemostatic imbalance. However, the mechanisms behind such hemostatic changes in severe patients with COVID-19 are still unclear.

Some previous articles focused on the association of COVID-19 severity with changes in primary and secondary hemostatic parameters, reporting that severe patients show longer prothrombin time (PT) and higher D-dimer values, with a lower platelet count.[5,11,12,43–45] Similar results were found in nonsurvivors to COVID-19 as compared with survivors. Among 183 hospitalized patients with COVID-19, it has been documented that 71.4% of nonsurvivors have overt disseminated intravascular coagulation (DIC) as compared with only 0.6% of survivors.[46,47] The presence of consumption coagulopathy among critically ill patients with SARS-CoV-2 infection may be in line with the observed changes in primary and secondary hemostatic parameters. The

pathogenesis of DIC is complex and multifactorial, and the "cytokine storm" described in ICU patients with SARS-CoV-2 infection may somehow contribute to its development.[48] However, many patients with severe COVID-19 may not fulfill the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC,[49] as coagulopathy seems to have its peculiar features among these patients. For instance, thrombocytopenia is less pronounced in severe COVID-19 patients as compared with sepsis-related DIC, while D-dimer levels are particularly high.[50] Moreover, although hyperfibrinogenemia is a common finding in COVID-19 patients, low fibrinogen levels have also been documented in nonsurvivors.[48]

Overall, based on available data, it can be hypothesized that the coagulopathy observed in severe COVID-19 may be a combination of a low-grade DIC with its own features and a localized pulmonary thrombotic microangiopathy.[50]

Considering the high thrombotic risk of COVID-19 patients, further specifically designed studies are needed to better address the issue of the hemostatic changes associated with COVID-19 severity. This could allow for a better understanding of the pathogenesis of this potentially fatal complication. Moreover, given the unknown long-term outcomes of COVID-19 and the increasing amount of literature data suggesting the presence of residual chronic disability and rehabilitation needs among survivors,[51–57] it is compelling to identify new biomarkers related to the disease to timely predict its clinical progression and to adequately manage critical patients even after the acute phase (e.g., general ward, rehabilitation centers, and home).[58]

In the meantime, in all hospitalized COVID-19 patients, following the WHO and ISTH indications,[59–61] prophylactic low-molecular-weight heparin (LMWH) or subcutaneous unfractionated heparin (UFH) should be considered.

Nevertheless, despite the lack of evidence supporting the prescription of high-dose prophylactic regimens, which may conversely increase the bleeding risk (particularly in patients with liver and renal impairment), the high rate of VTE reported during adequate thromboprophylaxis deserves to be considered and further investigated.[62] The fact that some authors suggested the use of therapeutic doses in all hospitalized patients with COVID-19 even in the absence of randomized trial evidence[25] reflects the belief in the medical community that standard thromboprophylaxis may be inadequate in the presence of such a strong prothrombotic switch.

Some potential limitations of our meta-analysis should be discussed. First, we have to consider that most included studies had a retrospective design and few studies ($n = 5$) enrolled consecutive COVID-19 patients undergoing imaging tests (Doppler ultrasound and/or computed tomography angiography) for VTE screening. Considering that symptoms of respiratory failure from COVID-19 are difficult to separate from those of PE, the fact that most studies based the execution of imaging tests on signs and symptoms of VTE may contribute to the significantly high heterogeneity affecting our results. However, although we could not definitively establish sources of such heterogeneity, our findings were substantially confirmed by appropriate sensitivity and subgroup analyses. In particular, we extended our results analyzing studies systematically performing thrombosis screening in all enrolled patients, showing a fourfold increase in DVT diagnosis rate. This might support the hypothesis that a strict screening of thromboembolic complications in all COVID-19 patients is needed. Moreover, the impact of clinical and demographic variables on results was evaluated by means of meta-regression models. Finally, we excluded the presence of publication bias by using different methods.

Conclusion

Results of the present meta-analysis show that the rate of VTE in COVID-19 patients is not negligible and claims the attention on the need of adequate screening procedures and antithrombotic strategies to manage VTE. Failure of prevention and interventional strategies for the prothrombotic state of severe COVID-19 patients may dramatically impact their prognosis. While waiting for data from a larger number of studies, the high thromboembolic risk of COVID-19 patients should be considered to timely predict and manage the long-term outcomes of these patients with potentially disabling and fatal complications.

Conflict of Interest
None.

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