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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Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: A systematic review with meta-analysis

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ABSTRACT

Background: Many studies confirmed an association between COVID-19 and venous thromboembolism (VTE). Whether the risk of VTE significantly differed between COVID-19 cohorts and non-COVID-19 cohorts with similar disease severity remains unknown.
Objectives: The aim of this systematic review with meta-analysis was to compare the rate of VTE between COVID-19 and non-COVID-19 cohorts with similar disease severity.
Methods: A systematic literature search (MEDLINE, Embase and Google Scholar) was conducted from January 1, 2020 to March 31, 2021 to identify studies reporting VTE in COVID-19. Relative risks (RR) were estimated for the effect measure with 95% confidence intervals.
Results: Seven studies (41,768 patients) evaluated VTE in COVID-19 cohorts compared to non-COVID-19 cohorts. The overall risk of VTE (RR 1.18; 95%CI 0.79–1.77; p = 0.42; I^2 = 54%), pulmonary embolism (RR 1.25; 95%CI 0.77–2.03; p = 0.36; I^2 = 52%) and deep venous thrombosis (RR 0.92; 95%CI 0.52–1.65; p = 0.78; I^2 = 0%) did not significantly differ between COVID-19 and non-COVID-19 cohorts. However, subgroup analyses suggested an increased risk of VTE amongst CODID-19 versus non COVID-19 cohorts when only patients hospitalized within the intensive care unit (ICU) were considered (RR 3.10; 95%CI 1.54–6.23), which was not observed in cohorts of predominantly non-ICU patients (RR 0.95; 95%CI 0.81–1.11) ($P_{interaction}$ = 0.001).
Conclusion: There was no signal for a difference in VTE in COVID-19 cohorts compared to non-COVID-19 cohorts, except for the subgroup of patients hospitalized in the ICU. These results should be viewed as exploratory and further studies are needed to confirm these results.

1. Introduction

In the early stages of the coronavirus disease 2019 (COVID-19) pandemic, pulmonary vascular abnormalities were reported on chest computed tomography (CT) of patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Subsequent reports suggested a high incidence of venous thromboembolism (VTE), reaching up to 6–69% in cohorts of critically ill patients [2,3]. This amazingly high risk of COVID-19-associated VTE was attributed to the cytokine storm and hyperinflammation frequently observed in these patients, resulting in sepsis-induced coagulopathy, disseminated intravascular coagulation [4], platelets dysfunction [5], endothelialitis, in-

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situ thrombosis and micro-thrombosis [6]. Since then, many studies confirmed an association between COVID-19 and VTE [7]. In an attempt to prevent VTE, several studies evaluated high-dose prophylaxis or even therapeutic anticoagulant doses in patients hospitalized for COVID-19 [8–10]. Despite the lack of quality published evidence, many institutional protocols even adopted intermediate- or therapeutic intensity dose strategy for thromboprophylaxis based on local experience and the assumption of a significant risk for VTE [11,12].

It is noteworthy, however, that both human and animal studies have shown that pulmonary thrombosis is common in sepsis-induced acute respiratory distress syndrome (ARDS) [13], pneumonia [14,15] and severe influenza infections [16], with the complex interplay of inflammatory and coagulation abnormalities contributing to the phenomenon of immunothrombosis [17]. Whether the high-risk of VTE reported in these COVID-19 series is specifically related to the SARS-CoV-2 tropism for the endothelium and subsequent coagulopathy, or is partly explained by inherent bias remains elusive. The aim of this systematic review with meta-analysis was thus to assess whether the risk of VTE significantly differed between COVID-19 cohorts and non-COVID-19 cohorts with similar disease severity.

2. Methods

The methods of this systematic review and meta-analysis are in accordance with "Cochrane Handbook for Systematic Reviews of Interventions" [18]. We wrote this report according to the recommendations of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [19] and the referred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [20].

2.1. Search strategy

This is a sub-analysis of our protocol registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO, registration No. CRD42020183842) that aimed to determine the prevalence of thrombotic events in patients with COVID-19 [7]. We initially searched MEDLINE, Embase and Google Scholar between January 1, 2020 and September 30, 2020. The grey literature was explored. There was no restriction on the language and the type of publication. Literature search was updated for this sub-analysis up to March 31, 2021.

2.2. Study selection

In the primary analysis, we included studies presenting these criteria: i) cohort of >10 patients, ii) patients with COVID-19 (positive reverse transcription polymerase chain reaction or positive CT-scan in patients with suggestive gestalt); iii) data reporting one of the outcomes of interest. For this subanalysis, we identified case-control studies comparing the rate of VTE in COVID-19 and non-COVID-19 patients. Two reviewers (B.K.T and J.C.L.) independently reviewed titles and abstracts of all articles related to the subject, as well as full papers when pertinent for a final decision concerning its inclusion in the meta-analysis. Two reviewers (V.M. and J.C.L.) independently extracted relevant information from all selected papers. Disagreements were resolved by consensus or by consulting a third reviewer (S.P.).

2.3. Outcomes

The outcome for the sub-analysis was the rate of VTE in COVID-19 cohorts compared to non-COVID-19 cohorts. VTE included pulmonary embolism (PE) and/or deep venous thrombosis (DVT). VTE could be diagnosed by symptomatic or systematic testing. The rate of PE only and DVT only were also individually assessed.

2.4. Assessment of methodological quality

The risk of bias of the selected studies was evaluated independently by two reviewers (V.M. and S.P.) using the methodological index for non-randomized studies (MINORS) for observational studies [21]. Publication bias was evaluated visually by a funnel plot. The strength of the body evidence was evaluated independently by two reviewers (V.M. and S.P.) for each outcome according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [22].

2.5. Statistical analysis

Analyses were performed using the Review Manager (*Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*). The meta-analysis comparing the rate of VTE in COVID-19 cohorts to non-COVID-19 cohorts was conducted using the Mantel-Haenszel method based on a random-effects model. Relative risks (RR) were estimated with a 95% confidence intervals (CI) and a p value. A p value <0.05 was considered statistically significant. Forest plots were created. Statistical heterogeneity was identified by using I^2. $I^2 > 50\%$ was considered as substantial statistically heterogeneity. We also planned subgroup analyses to investigate sources of heterogeneity in the main analysis according to hospitalization settings (cohorts of ICU patients only vs predominantly non-ICU patients), presence or absence of ventilator support, study types (prospective vs retrospective) and presence or absence of thromboprophylaxis.

3. Results

3.1. Characteristics of the selected studies

We identified 4080 citations of which 167 were retained for full-text evaluation. Seven articles [23–29] (41,768 patients) reported the rate of VTE in COVID-19 cohorts compared to non-COVID-19 cohorts (Fig. 1). The characteristics of the studies are reported in Table 1. Three were prospective studies [23,27,29] and 4 were retrospective studies [24–26,28]. One study matched COVID-19 and non-COVID-19 patients using a 1:3 ratio [23]. Three studies included 100% patients from the intensive care unit (ICU) [23,25,29] whereas 2 studies enrolled the patients from the emergency department [26,27] and 2 studies did not reported it [24,28]. One study compared patients with ARDS related or not to COVID-19 [23], whereas COVID-19 patients were compared to patients with community-acquired pneumonia [24], influenza [25,28] and non-COVID-19 infections [26–29]. Within each study, groups were comparable in terms of ICU admission rates, sex, age and methods for VTE diagnosis. Patients were all on prophylactic anticoagulation in 2 studies [24,25], 22–38% of the patients were on therapeutic anticoagulation in 2 studies [23,27], 1 study [29] included patients on prophylactic, intermediate or therapeutic dose anticoagulation and 2 studies [26,28] did not report this data. VTE was diagnosed based on symptomatic testing in 4 studies [23,25–27], in selected patients considered at high-risk based on institutional standards in 1 study [24], in symptomatic testing for PE and systematic screening for DVT in 1 study [29] and was not reported in 1 study [28].

3.2. VTE occurrence

The cumulative relative risk (RR) estimate for VTE amongst COVID-19 patients was 1.18 (95%CI 0.79–1.77; $p = 0.42$; $I^2 = 54\%$) compared to non-COVID-19 patients. (Fig. 2A). Consistently, no statistically significant results were seen in patients with COVID-19 compared to non-COVID-19 patients in regards of PE only (RR 1.25; 95%CI 0.77–2.03; $p = 0.36$; $I^2 = 52\%$) (Fig. 2B) and DVT only (RR 0.92; 95%CI 0.52–1.65; $p = 0.78$; $I^2 = 0\%$) (Fig. 2C). Subgroup analyses, suggested an increased risk of VTE amongst COVID-19 versus non-COVID-19 patients hospitalized within the ICU (RR 3.10; 95%CI 1.54–6.23), which was not

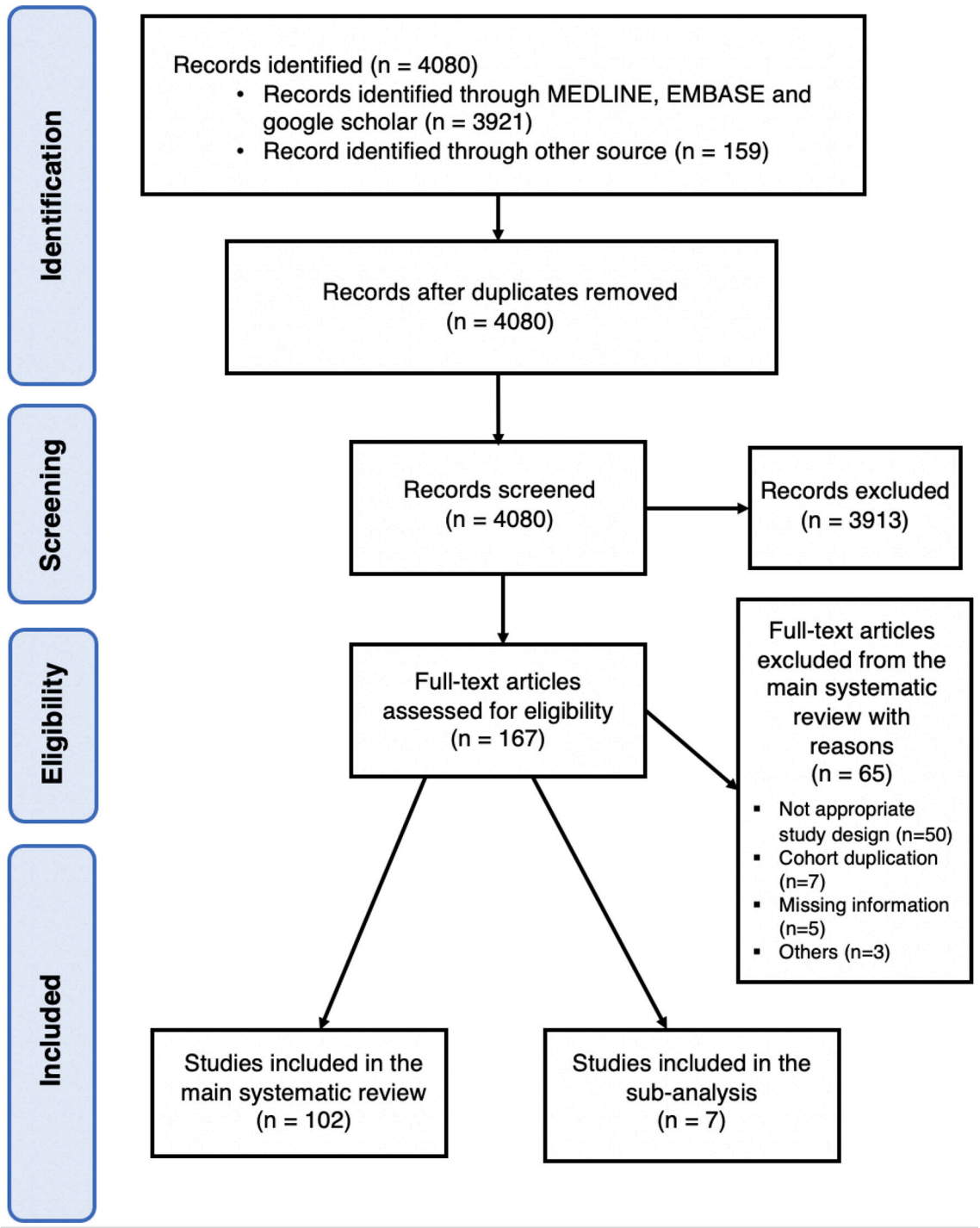


Fig. 1. Study selection.

observed in cohorts of predominantly non-ICU patients (RR 0.95; 95%CI 0.81–1.11) ($P_{interaction}$ = 0.001). The risk of VTE in COVID-19 versus non-COVID-19 patients was also increased in prospective studies only (RR 2.74; 95%CI 1.18–6.40) (Table 2). However, no difference was seen in regards of the presence or absence of ventilator support and presence or absence of thromboprophylaxis.

3.3. Risk of bias within studies, publication bias and quality evidence

The median MINORS score was 12 (range 9–19) for the studies comparing VTE in COVID-19 cohorts compared to non-COVID-19 cohorts (Table S1). Visual inspection of the funnel plots of VTE occurrence were exploratory given the limited number of studies and yielded no publication bias (Fig. S1). The strength of evidence based on the GRADE methodology was considered very low for VTE occurrence (Table S2).

4. Discussion

The present meta-analysis suggests that while VTE are frequent amongst patients hospitalized for COVID-19, the VTE occurrence appears comparable between COVID-19 patients and those with non-COVID-19 infections. However, patients with COVID-19 hospitalized in the ICU may to be at the highest risk of developing VTE, being significantly higher than non-COVID-19 patients hospitalized in the ICU.

Table 1
Characteristics of studies evaluating VTE in COVID-19 cohorts.

Study	Country	Design	COVID-19 status	Patients in ICU during the study (%)	Number of patients	Mean follow-up (days)	Male sex (%)	Median age (Q1;Q3)	Diagnosis of thrombotic event	Prophylactic dose A/C (%)	Intermediate dose A/C (%)	Therapeutic dose A/C (%)	D-dimer (mg/L)	Mortality
Dalager-Pedersen et al. (2021) [28]	Denmark	Retrospective cohort study	COVID-19	NR	1540	30	56.6	72.0 (58.0;81.0)	NR	NR	NR	NR	NR	NR
			Non-COVID-19	NR	26,131	30	50.1	68.0 (48.0;78.0)	NR	NR	NR	NR	NR	NR
			Influenza	NR	9599	30	48.8	70.0 (59.0;80.0)	NR	NR	NR	NR	NR	NR
Freund et al. (2020) [26]	France, Spain, Belgium, Italy, Chile, Canada	Retrospective cohort study	COVID-19	0	974	NR	48.0[a]	61.0 ± 19.0[a,b]	Symptomatic testing	NR	NR	NR	NR	NR
			Non-COVID-19	0	2279	NR	48.0[a]	61.0 ± 19.0[a,b]	Symptomatic testing	NR	NR	NR	NR	NR
Helms et al. (2020) [23]	France	Prospective (COVID-19) and "historical prospective" (non-COVID-19) cohort study	COVID-19 ARDS	100	77[c]	7[d]	81.8	68.0 (61.0;75.0)	Symptomatic testing	77.9	0.0	22.1	NR	NR
			Non-COVID-19 ARDS	100	145[c]	NR	77.2	72.0 (61.0;80.0)	Symptomatic testing	75.9	0.0	24.1	NR	NR
Mei et al. (2020) [24]	China	Retrospective cohort study	COVID-19	NR	256	NR	51.2	55.5 (range 0.5–87.0)	Testing when Padua score > 4	100[e]	0.0	0.0	0.510	16
			Community acquired pneumonia	NR	360	NR	58.6	61.0 (range 15.0–95.0)	Testing when Padua score > 4	100[e]	0.0	0.0	0.590	14
Pellegrini et al. (2021) [29]	Brazil	Prospective cohort study	COVID-19	100	57	NR[f]	52.6	56.0 ± 13.0[b]	Symptomatic testing for PE and systematic screening for DVT	19.3	77.2	3.5	0.001	25
			Non-COVID-19	100	13	NR[f]	53.8	57.0 ± 20.0[b]	Symptomatic testing for PE and systematic screening for DVT	53.8	23.1	2.7	0.002	3
Poissy et al. (2020) [25]	France	Retrospective cohort study	COVID-19	100	107	NR	NR	NR	Symptomatic testing	100[g]	0.0	NR	NR	NR
			Influenza	100	40	NR	NR	NR	Symptomatic testing	100[g]	0.0	NR	NR	NR
Rieder et al. (2020) [27]	Germany	Prospective cohort study	COVID-19	16.3	49	30	61.2	60.0 (48.5;71.5)	Symptomatic testing	NR	NR	24.3	1.100	3
			Non-COVID-19	7.1	141	30	50.4	60.0 (43.5;76.5)	Symptomatic testing	NR	NR	37.6	0.800	7

A/C: anticoagulation; COVID-19: coronavirus disease 2019; DVT: deep venous thrombosis; ICU: intensive care unit; NR: not reported; PE: pulmonary embolism; VTE: venous thromboembolism.

[a] Data for the whole studied population.

[b] Mean ± standard deviation.

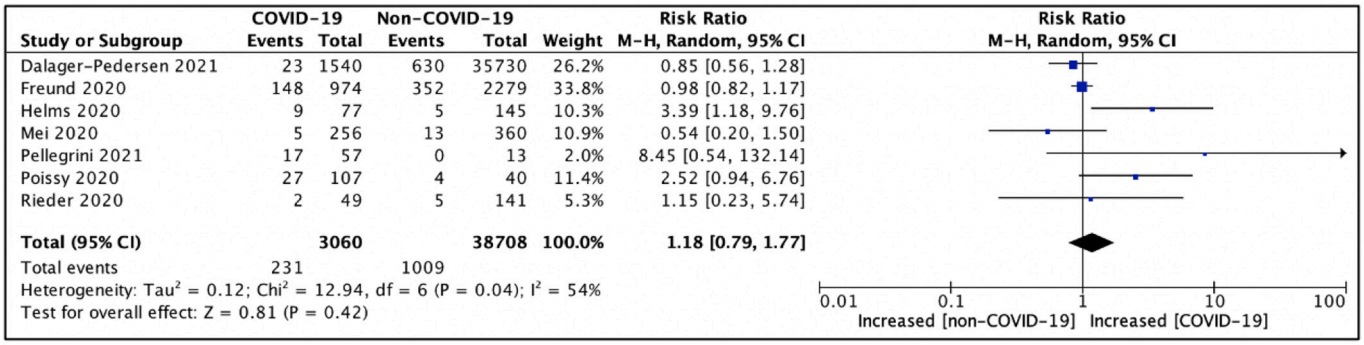
[c] COVID-19 and non-COVID-19 patients were matched in a ratio 1:3 based on the propensity scores generated by the multivariable logistic regression model. Independent variables used in the multivariable logistic regression are age, sex, medical history of malignancies, cardiovascular diseases, cerebrovascular diseases, venous thrombo-embolic event, immune diseases, chronic liver diseases, chronic renal diseases, respiratory diseases, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment Score, PaO2/FiO2 on ICU admission, anticoagulant treatment and extracorporeal membrane oxygenation.

[d] At least.

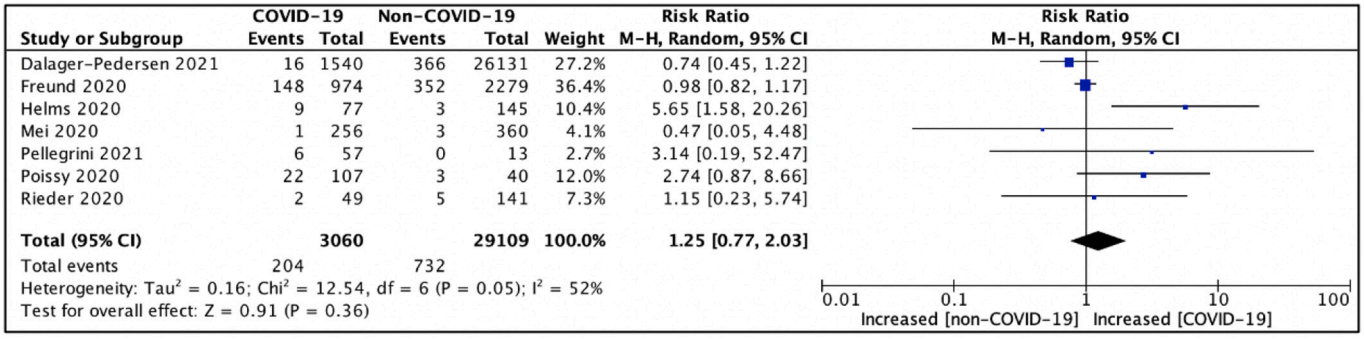
[e] Mechanical intermittent pneumatic compression device if contraindicated to anticoagulants.

[f] Follow-up until hospital discharge or death.

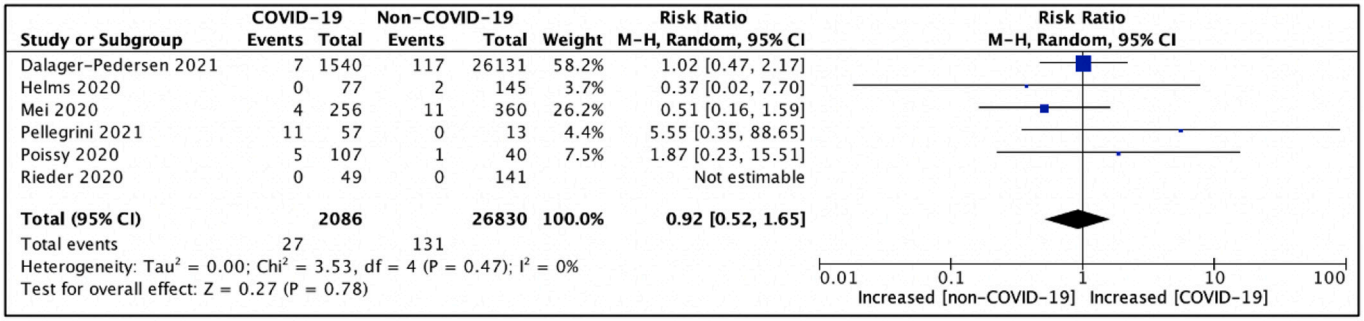
[g] 2 patients were on therapeutic anticoagulation for a history of DVT and atrial fibrillation at the time of PE diagnosis, not mentioned the percentage of therapeutic anticoagulation in patients without PE diagnosis.



A. Venous thromboembolism.



B. Pulmonary embolism only.



C. Deep venous thrombosis only.

Fig. 2. Forest plot and relative risk (RR) for venous thromboembolism (A), pulmonary embolism only (B) and deep venous thrombosis only (C) in COVID-19 cohorts compared to non-COVID-19 cohorts.

Severe COVID-19 requiring ICU admission may thus be a risk factor for developing VTE.

In the early stages of the COVID-19 pandemics, anecdotal reports described cases of PE diagnosed concomitantly with COVID-19 [1,30]. Disseminated intravascular coagulation, microthrombi in different organs including the pulmonary circulation [31] and VTE were subsequently documented in a significant proportion of critically ill patients. High levels of D-dimers were repeatedly shown to be associated with the need for ICU admission and mortality amongst COVID-19 patients [32]. This is not surprising since lung coagulopathy is relevant in the pathogenesis of ARDS [33]. The cytokines storm and pulmonary microthrombi observed with COVID-19 are thus consistent with the immunothrombosis model, which highlights the bidirectional relationship between the immune system, inflammation and thrombin generation during severe infection [17]. Importantly, these phenomena may be enhanced in COVID-19 patients in whom the occurrence of VTE appeared to occur at a higher rate when compared to patients with similarly severe ARDS and infections. This finding thus supports early reports suggesting extremely high incidence of VTE in critically ill patients with COVID-19 [2,34–36].

Severe COVID-19 commonly presents an atypical form of ARDS with significant dissociation between relatively well-preserved lung mechanics and severe hypoxemia, for which the loss of lung perfusion regulation and hypoxic vasoconstriction has been proposed as potential explanations [37]. However, since the risk of VTE gained significant attention of the medical community, this may have led to an increased reliance on chest CT to search for other mechanisms. Moreover, preliminary reports described pulmonary vascular abnormalities on chest CT [1], where vascular thickening was significantly associated with COVID-19 compared to non-COVID-19 pneumonia [38]. It is therefore possible that chest CT being more routinely performed in COVID-19 patients may have led to VTE overdiagnosis or distal PE for which the clinical relevance remains uncertain. In addition to confirmation bias, selective reporting is also plausible in the context of the rapidly evolving publications on COVID-19 over the last year. On the other side, an underreporting of VTE amongst patients with COVID-19 infection hospitalized in the non-ICU setting cannot be excluded, which could have explained that overall VTE rates in predominantly non-ICU patients

Table 2
Subgroup analysis to explore sources of heterogeneity in estimate of venous thromboembolism occurrence.

	Number of studies	Number of patients	Risk relative (95% confidence interval)	I^2	p-value ($p_{interaction}$)
Study settings					
ICU only	3	439	3.10 (1.54–6.23)	0%	0.001
Predominantly non-ICU	4	41,329	0.95 (0.81–1.11)	0%	0.26
Ventilator support					
Presence	4	475	1.72 (0.63–4.67)	53%	
Absence	5	41,293	0.96 (0.78–1.18)	7%	
Type of studies					0.03
Prospective	3	482	2.74 (1.18–6.40)	1%	
Retrospective	4	41,286	0.97 (0.70–1.35)	44%	
Anticoagulation					0.06
Prophylactic, intermediate and/or therapeutic dose	3	482	2.74 (1.18–6.40)	1%	
Prophylactic dose only	2	763	1.17 (0.26–5.32)	78%	
Not reported	2	40,523	0.96 (0.82–1.13)	0%	

were comparable between COVID-19 and non-COVID-19 patients.

Importantly, many institutional protocols adopted aggressive thromboprophylaxis for severe COVID-19 patients. Heparins also have non-anticoagulant properties, including anti-inflammatory [39] antiviral [40] and protective effects on the pulmonary endothelium [41]. Nonetheless, current guidelines recommend the use of thromboprophylaxis at a prophylactic dose in all COVID-19 patients admitted to the hospital [42–45] while awaiting for results of ongoing studies evaluating intermediate and therapeutic anticoagulants dose for the prevention of VTE [46]. This approach appears reasonable in the context of a significant proportion of COVID-19 patients, both on prophylactic and therapeutic anticoagulation, exhibiting major bleeding [47]. The recruitment of critically ill COVID-19 patients were also prematurely stopped for futility reasons in ongoing anticoagulation trials. More importantly, while immunothrombosis is incontestably implicated in ARDS pathophysiology and VTE are quite prevalent in patients with severe COVID-19 and non-COVID-19-related ARDS, previous attempts to translate the beneficial effects of anticoagulation documented in animal models of ARDS and severe sepsis failed to demonstrate survival benefit in humans [48,49]. These results may reflect the complex interplay between inflammation, immune factors and endothelialitis that contribute to immunothrombosis and VTE in severe COVID-19 [6,50].

We acknowledge that our meta-analysis presents some limitations. First, all the included studies were observational studies and case series resulting in a certain risk of bias evaluated by the MINORS tools [21] and a very low strength of evidence based on the GRADE methodology [22]. The different cohorts were also heterogenous. Third, only seven studies were included in the evaluation of VTE in COVID-19 cohorts compared to non-COVID-19 cohorts although more than 100 publications have been published on VTE occurrence in COVID-19 patients. Despite the fact that the present meta-analysis incorporated data from a large study population, this finding confirms that a minority of studies assessed whether COVID-19 was specifically associated with VTE in comparison to non-COVID infections of similar severity. Fourth, VTE rates amongst ICU (22.0%) in the present meta-analysis were comparable to those previously reported in recent meta-analyses on COVID-19, occurring in 23.2% (95%CI 17.5–29.6%) [7]. Conversely, the rate of VTE observed amongst non-ICU patients (6.2%) was were slightly lower compared to recent meta-analysis (9.0%; 95%CI 6.9–11.4%) [7]. Accordingly, an increased risk of VTE in non-ICU patients with COVID-19 compared to non-COVID infections could not be excluded. Finally, the follow-up duration was short for most included studies. Whether these results are representative of the VTE risk for patients hospitalized for longer periods remains to be determined.

5. Conclusion

The present meta-analysis documented no signal for a difference in overall risk of VTE occurrence in COVID-19 cohorts compared to non-COVID-19 cohorts. However, subgroup analyses suggest an increased risk of VTE amongst COVID-19 patients hospitalized in the ICU. However, these results should be viewed as exploratory and further studies are needed to confirm our results and to evaluate the most appropriate thromboprophylaxis dosing in patients with COVID-19.

Author contributions

SP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. VM, BKT, SM, FP, MC and JCL contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. Specifically: V. Mai contributed to study design, completed the literature search, data collection, data analysis, data interpretation, and drafted the first version of the manuscript. B. K. Tan completed the literature search and data collection. S. Mainbourg contributed to data interpretation and revised the manuscript. F. Potus contributed to data interpretation and revised the manuscript. M. Cucherat contributed to data interpretation and revised the manuscript. J. C. Lega contributed to data collection, data interpretation and revised the manuscript. S. Provencher contributed to study design, literature search, data analysis, data interpretation and wrote and revised the manuscript.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vph.2021.106882.

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