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Thrombosis risk associated with COVID-19 infection. A scoping review

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ABSTRACT

Background: Infection by the 2019 novel coronavirus (COVID-19) has been reportedly associated with a high risk of thrombotic complications. So far information is scarce and rapidly emerging.
Methods: We conducted a scoping review using a single engine search for studies assessing thrombosis and coagulopathy in COVID-19 patients. Additional studies were identified by secondary review and alert services.
Results: Studies reported the occurrence of venous thromboembolism and stroke in approximately 20% and 3% of patients, respectively. A higher frequency seems to be present in severely ill patients, in particular those admitted to intensive care units. The thrombotic risk is elevated despite the use of anticoagulant prophylaxis but optimal doses of anticoagulation are not yet defined. Although an increase of biomarkers such as D-dimer has been consistently reported in severely ill COVID-19, the optimal cut-off level and prognostic value are not known.
Discussion: A number of pressing issues were identified by this review, including defining the true incidence of VTE in COVID patients, developing algorithms to identify those susceptible to develop thrombotic complications and severe disease, determining the role of biomarkers and/or scoring systems to stratify patients' risk, designing adequate and feasible diagnostic protocols for PE, establishing the optimal thromboprophylaxis strategy, and developing uniform diagnostic and reporting criteria.

1. Introduction

The World Health Organization (WHO) declared the 2019 novel coronavirus (SARS-CoV-2) a pandemic on March 11, 2019. The number of confirmed cases as of May 17 is over 4.5 million with over 300,000 confirmed deaths (https://www.who.int) [1]. Up to 14% of infected patients sustain interstitial pneumonia, and may evolve to acute respiratory distress syndrome requiring intensive care unit (ICU) admission, and may be accompanied by multiorgan failure [2].

Recent findings from a pooled analysis suggested that a prominent increase in D-dimer levels as a predictor of adverse outcomes was persistently seen in coronavirus disease 2019 (COVID-19) suggesting the presence of underlying coagulopathy [3]. There is increasing evidence that severe COVID-19 seems to be associated with pro-hemostatic state with a potential impact on thromboembolism risk, but the nature and extent of these abnormalities is not clear. Given the rapid emergence of new evidence we sought to conduct a scoping review of coagulopathy and thrombosis risk associated with COVID-19 infection with the aim of providing an overview of the current knowledge on this topic and potentially inform new areas of research.

2. Methods

The review is registered in Open Science Framework and the study protocol is publicly available (https://osf.io/zm2gk/). We conducted a literature search using a single search engine through PubMed using the Medical subject headings (MeSH) COVID, coronavirus, coagulopathy, disseminated intravascular coagulation, thrombosis, deep vein thrombosis, pulmonary embolism, venous thromboembolism and haemostasis, using Boolean operators. We also retrieved additional references from the guidelines of the International Society on Thrombosis and Haemostasis (ISTH) [4,5] and Thrombosis UK [6]. Additionally, preprint databases (Preprints.org, biorxiv.org) were also searched for papers accepted but not yet published and we also scanned all retrieved papers for additional references.

We included randomized control trials (RCTs), observational cohort studies (prospective or retrospective), case-control studies or case series that included adult participants with hospitalized COVID-19 infection

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and assessed thrombosis or coagulopathy. There was no language restriction.

Initially, broad screening was conducted according to title. Subsequently, all relevant abstracts were reviewed. In the end, all potentially included articles were reviewed in full length. Two reviewers (FA-A, SC) separately assessed the potentially included papers to verify eligibility. Discrepancies were resolved by a consensus or by a third reviewer (AL-L). Translation of included papers from Chinese to English was conducted with the use of Google Chrome's built-in translation tool.

The study outcome was a descriptive assessment of thromboembolism incidence and risk including deep venous thrombosis (DVT)/pulmonary embolism (PE), thromboprophylaxis strategy, risk of Disseminated Intravascular Coagulation (DIC) in COVID-19 infections, and the role of coagulation parameters in predicting the severity and mortality of the disease.

Although not part of the original protocol, given the data retrieved in the review we performed a meta-analysis of proportions for the frequency of VTE in order to further explore our findings. We estimated pooled proportions through a Freeman-Tukey transformation using fixed and random effects models. Sensitivity analyses were done by excluding studies with the highest and lowest proportions, studies including > 75% or < 75% of patients admitted to an intensive care unit. The analysis was done using MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

3.1. Search strategy

The initial search was conducted up to April 23. Fifty potentially included papers were initially screened. Following a title and abstract screening, a total of 25 studies were reviewed in full text. Of those, 16 studies fulfilled our eligibility criteria. The 7 excluded studies included 5 literature reviews/systematic reviews, and 2 duplicates. Of the final 16 included studies, 9 were cohort (8 retrospective and 1 prospective), 6 were case series/case reports, and 1 was an editorial letter. Fifteen of the included studies were in English and one was in Chinese, but the abstract was in English [7]. Because of the rapidly evolving nature of the topic, the search was updated up to May 12, 2020. Eventually, thirty additional papers were included after our initial screen identified through PubMed search and electronic alerts set in major medical journals and medical information services.

3.2. Coagulation markers

3.2.1. D-dimer

One of the earliest and commonest laboratory findings noted in COVID-19 patients requiring hospitalization was the marked elevation of D-dimer. A high D-dimer is nonspecific and often associated with various medical conditions such as infections, trauma, or even hospitalization; however, in the setting of COVID-19 infection, it has been consistently reported as a poor prognostic marker that is associated with critical course and higher mortality. A pooled analysis suggested that D-dimer values were higher in patients with severe COVID-19 than in those with milder forms and therefore, D-dimer measurement may be associated with evolution toward a worse clinical picture [3] although emerging evidence may suggest conflicting results.

The association of disease severity in COVID-19 infections with a higher D-dimer level was reported in a handful of studies summarized in Table 1. The first study that shed light on the association of the severity of COVID-19 infection with a high D-dimer level was a large retrospective study by Guan et al. that evaluated 1099 patients with COVID-19 infection. The study suggested that a cut-off point of 0.5 mg/L is more frequent in patients with severe disease than in those without (60% vs. 43%, p = 0.002) [8]. Subsequently, another retrospective study with 183 patients showed a higher cut-off in which D-dimer values were nearly 3.5-fold higher in those with severe disease than in those without (p < 0.001) [9]. Wang et al. conducted a single center retrospective study of 138 hospitalized patients; there was a 2.5 fold increase in D-dimer level in ICU patients (n = 36) compared to non ICU (n = 102) patients (p < 0.001) [10]. A prospective study (n = 41) reported almost five fold higher level of D-dimer in ICU patients versus non-ICU patients (median D-dimer level 2.4 mg/L [0.6–14.4] versus 0.5 mg/L [0.3–0.8], p = 0.0042) [11]. A small case series of seven patients with critical COVID-19 and acral ischemia presentation also reported that D-dimer increased progressively when COVID-2019 exacerbated [7]. A small prospective study from Italy reported higher baseline D-dimer levels in 16 patients with ARDS admitted to ICU [12]. However, new data showed conflicting evidence [13]. Based on a nationwide cohort including 2300 Chinese patients, the investigators developed and validated a clinical score to predict COVID-19 patients that would develop critical course requiring ICU admission. Among the 10 independent predictive factors, D-dimer was not included in the score. In fact, the mean D-dimer was lower in patients with critical illness.

With regards to association with mortality, several studies reported that a significantly elevated level of D-dimer was a predictor of death. In the study by Wang et al. 33 patients (5 non-survivors and 28 survivors) with complete clinical course were analyzed, and the dynamic profile of laboratory findings was tracked. In the non-survivors, D-dimer continued to increase and reached over 1000 mg/L until death occurred, whereas the level was almost normalized to below 500 mg/L in the survivors (p < 0.05) [10]. Similarly, Zhou et al. (n = 191) reported a significantly higher D-dimer of around 9-fold was seen in non-survivors as compared to survivors with severe disease (81% vs. 24%; p < 0.001) [14]. Furthermore, Tang et al. reported similar findings with a higher D-dimer being seen in non survivors (n = 21) (2.12 [0.77–5.27]) compared to survivors (n = 162) (0.61 [0.35–1.29]) (p < 0.001) [9]. Similarly, D-dimer was associated with disease severity in a study by Gao et al. [15]. More recently, a study summarized the clinical characteristics of 25 death cases with COVID-19 in Wuhan [16]. In 9 of 12 patients where the test readings were available, the last level of D-dimer measured was higher as compared to the first test. Finally, a recent Irish prospective study that assessed coagulopathy in Caucasian patients with COVID-19 [17] suggested the presence of significant coagulopathy in Caucasian patients that appears to be similar in magnitude to that previously reported in the Chinese cohorts. Similarly, D-dimer levels were significantly higher in non-survivors compared to survivors during the disease.

Overall, the studies consistently reported a significant increase in D-dimer. More importantly, the D-dimer increase was dynamic, meaning it seems to continue to rise as the disease progresses and reflected a prognostic indicator of mortality. However, most of the studies were retrospective except for two prospective studies that included a small number of patients [11,12]. Furthermore, many of those papers were conducted at a single center. Limitations of evidence include: 1) all studies were limited to a single ethnic population, and extrapolation of this data to other populations might not be accurate, and 2) except for the study by Tang et al. which had negative findings, none of the studies were designed to assess the coagulopathy as a predictor of outcomes in patients with severe COVID-19 infections.

3.2.2. Prothrombin time

Five studies reported on prothrombin time with COVID-19 infection. Wang et al. reported a prolonged prothrombin time (13.0 s [IQR, 12.3–13.7]) in 80 patients (58%) in patients with COVID-19 pneumonia with no statistically significant difference between ICU and non-ICU patients (p = 0.37) [10]. On the other hand, Huang et al. reported a slightly higher prothrombin time in ICU patients (median prothrombin time 12.2 s [IQR 11.2–13.4]) than non-ICU patients (median prothrombin time 10.7 s [9.8–12.1], p = 0.012) [11].

With regards to association with mortality, Zhou and colleagues reported a significantly higher prothrombin time (> 16 s) in non-

Table 1
D-dimer association with severity in COVID-19 infection.

		Patients with non-severe disease			Patients with severe disease			
Study	D-dimer measurement	Total (n)	Patients with D-dimer above the cut off [n,(%)]	D-dimer	Total (n)	Patients with D-dimer above the cut off [n,(%)]	D-dimer	p
Guan et al. [8]	Cut off: 0.5 mg/L	451	195 (43.2)	–	109	65 (59.6)	–	0.002
Wang et al. [10]	Median (mg/L)	102	–	166	36	–	414	< 0.001
Huang et al. [11]	Median (mg/L)	28	–	0.5	13	–	2.4	0.0042
Gao et al. [15]	Median (mg/L)	28	–	0.2 (IQR: 0.2–0.3)	15	–	0.5 (IQR: 0.3–0.9)	< 0.05
Liang et al. [13]	Mean (SD)	1459	–	26.3 (144.8)	131	–	19.1 (70)	NS

NS, non significant; IQR, interquartile range; SD, standard deviation.

survivors (n = 54) compared to survivors (n = 137) (13% vs. 3%; p = 0.0004) [14]. Another study echoed that association in which significantly longer prothrombin time were found in non-survivors (n = 21) compared to survivors (n = 162) on admission (p < 0.001) [9].

However, Fogarty and colleagues found no significant difference in PT between survivors and no-survivors on admission [17]. Unlike Chinese studies, no progressive increase in PT was observed in the adverse prognostic group.

3.2.3. Platelet count

Several studies reported no difference in platelets count between ICU and non-ICU patients [8,10,11]. In the study by Guan et al. around half (46.6%) of patients with one or more composite outcomes (ICU admission, the use of mechanical ventilation, or death) had a platelet count < 150 [8]. With regards to mortality, Zhou et al. reported that a platelet count of < 100 was more frequently seen in non-survivors than survivors (20% vs 1%) [14]. In the prospective Irish study by Fogarty et al., platelet counts were within the normal range in 83.1% of patients with a platelet count < 100 × 109/L observed in only 5 patients on admission [17]. Overall, the platelet count was mild-moderately lower in severe COVID-19 infections, although a recent Chinese retrospective study in 1476 patients reported an in-hospital mortality of 92.1% for those with a platelet count between 0 and 50. The relative risk was of 3.42 (95% confidence interval [CI] 2.36–4.96) for platelet counts between 100 and 150, 9.99 (95% CI 7.16–13.94) for counts between 50 and 100, and 13.68 (95% CI 9.89–18.92) for platelets between 0 and 50 [18].

3.2.4. Antiphospholipid antibodies

A small case series from Wuhan, China reported the presence of Anticardiolipin IgA, Anti-beta2-glycoprotein IgA and IgG positivity in 3 patients with stroke [19]. While intriguing, it should be noted that IgA subtypes of antiphospholipid antibodies have not been demonstrated to have a role in thrombophilia. In addition, a case series in France identified lupus anticoagulant positivity in 25 out of 56 patients (45%) admitted with COVID-19. Anti-cardiolipin and anti-beta-2-glycoprotein IgG and IgM were detected in 5 out of 50 tested patients (10%) with 3 of these being associated with lupus anticoagulant. No comment was made as to whether any of these patients had thrombotic events [20]. The role of the presence of antiphospholipid antibodies is yet to be determined as it is known that they can be detected in patients with acute infections [21].

3.3. Coagulopathy

3.3.1. Disseminated Intravascular Coagulation (DIC)

Two retrospective studies from China reported on DIC in survivors versus non-survivors. Both studies defined DIC according to the diagnostic criteria of the International Society on Thrombosis and Haemostasis (ISTH) [22]. In the single center study by Ai T et al., 15 of 21 non-survivors (71%) were classified as having overt-DIC (≥5 points) any time during follow-up, whereas only 1 of 162 survivors (0.6%) met these criteria (p < 0.001) [23]. Tang et al. reported that the vast majority of COVID-19 patients who died during hospital stay fulfilled the criteria for diagnosing DIC: 71.4% of non survivors (n = 21) versus 0.6% of survivors (n = 162) [9]. Interestingly, researchers also noted an initial increase in fibrinogen with advanced COVID-19; however, the level tended to be significantly lower in non-survivors and was associated with a decrease in antithrombin levels. This observation might indicate that a hypercoagulable status associated with the course of severe COVID-19 infection could be related to prognosis. A second study reported a significantly higher incidence of DIC reported among non survivors compared to survivors (6.4% vs. 0, p = 0.006), however, the study did not provide a DIC definition [24]. Moreover, in the study by Fogarty et al., despite the increased D-dimer level, DIC was not evident [17]. Another study reported DIC in 2.1% of 388 patients, with no bleeding complications but a high mortality (88%) [25]. Other 2 studies have reported an association of DIC with disease severity but they have serious methodological limitations [7,8].

Overall, studies have reported marked derangement in haemostasis in non survivors with markedly elevated D-dimers, prolonged prothrombin time, and increase in fibrin degradation products. However, modest degree of thrombocytopenia and high fibrinogen levels were observed with advanced COVID-19 disease as opposed to significant reduction in those levels with DIC seen with sepsis [6]. This finding was echoed in a recent Italian study in which the pattern of prothrombotic coagulopathy and DIC was different from that in sepsis, where platelet count is usually decreased, and the prothrombin time is prolonged with associated hemorrhagic tendency [12]. Therefore, DIC associated with severe COVID-19 infection could represent a distinct entity of coagulopathy.

3.3.2. Thrombotic microangiopathy

Limited evidence from case reports has suggested that pulmonary microvascular thrombosis plays a role in the ARDS and respiratory failure associated with COVID-19 pneumonia based on lung biopsies/autopsies. Lou et al. recently published a case report of lung biopsy findings from a patient with COVID-19 pneumonia. The lung biopsy showed pulmonary interstitial fibrosis, hemorrhagic pulmonary infarcts, small vessel hyperplasia, luminal stenosis and microthrombi [26].

Furthermore, Fox et al. reported a small series of autopsies in the United States, with the cause of death being COVID-19 infection [27]. All lung sections showed diffuse alveolar damage, with a mild to moderate mononuclear response consisting of notable CD4+ aggregates around thrombosed small vessels, and significant associated hemorrhage. Therefore, the process of thrombotic microangiopathy restricted to the lungs was proposed as an additional factor contributing to the death in those patients.

3.4. Thrombotic manifestations

3.4.1. Venous thromboembolic disease

The presence of microthrombotic disease in pulmonary arteries [26] plus findings of coagulopathy associated with COVID-19 prompted physicians to consider Pulmonary Embolism (PE) as etiology of patients with acute respiratory deterioration. In case reports of COVID-19 patients, PE was identified in patients with no VTE risk factors [28]. A case series of post-mortem autopsies found that venous thromboembolism was present in 7 of 12 (58%) patients with COVID-19, with PE being the direct cause of death in 4 (33%) [29]. Similarly, alveolar damage on autopsy was reported in 2 more studies [30,31]. Zhang et al. reported pulmonary microvascular thrombosis and necrosis in mediastinal lymph nodes and the spleen, and small vessel thrombosis in multiple organs in 4 patients with COVID-19. The microvascular thrombi were characteristic to COVID-19 infection as opposed to SARS1 infection [31].

Early data demonstrated the possibility of increased incidence of thrombosis in COVID-19 patients, particularly in critically ill patients. A single-centre retrospective observational review of 138 COVID-19 patients admitted in Shanghai, China found that deep vein thrombosis (DVT) was diagnosed in 4 patients (2.9%). Of these, 3 were critically ill. Critically ill patients were defined as being admitted to the ICU and requiring mechanical ventilation or requiring at least 60% FiO2 to maintain oxygen saturation at an acceptable level. In total, 15 patients were defined as critically ill, which meant that in this small sample size, VTE was present in 20% of critically ill patients. All 4 patients who developed DVTs did so despite use of routine thromboprophylaxis with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) [32].

A case series from France analyzed the first 107 consecutive COVID-19 patients admitted to the ICU of a single centre and compared rates of PE to that in patients admitted to the same ICU one year prior, and to that in patients admitted with influenza. At time of analysis, 22 (20.6%) of the COVID-19 patients had PE, with a median time to diagnosis of 6 days. In comparison, the general ICU population one year prior and the influenza population had PE rates of 6.1% and 7.5%, respectively. The cumulative incidence of PE at 15 days in the COVID-19 population was 20.4%. Of the 22 patients diagnosed with PE, 20 were receiving prophylactic doses LMWH or UFH, while one patient was on fluindione with therapeutic INR, and another was on therapeutic UFH for atrial fibrillation [33].

A more recent and larger study reviewed COVID-19 patients admitted to the ICU at three centres in the Netherlands (n = 184) [34]. In this study, patients were enrolled from the time they were admitted to ICU. Patients were followed until they were discharged from ICU, died, or until the study period ended. All patients received standardized doses of subcutaneous nadroparin although the exact dose regimen varied by centre. One centre used 2850 international units (IU) per day, or 5700 IU per day if body weight was > 100 kg. The second centre used 5700 IU per day up until 4 April 2020, at which points all patients were switched to 5700 IU BID. The third hospital used 2850 IU per day, or 5700 IU per day if body weight was > 100 kg, however, on 30 March 2020, they switched to using 5700 IU per day for all patients. In this study, the composite outcome was defined as any of: DVT, PE, ischemic stroke, myocardial infarction, or systemic arterial thrombosis and all events were symptomatic. The initial study reported 31 events (25 PE, 3 DVT, and 3 strokes) representing a cumulative incidence of 31% but affecting 16.8% of the patients. It should be noted that 7 of the 25 PE were limited to subsegmental arteries.

This study was recently updated with data analysis being extended to April 22nd. Using competing risk analysis, the study confirmed the results previously reported. During the added time, 44 new thrombotic events were diagnosed (40 PE, 2 strokes, and 2 peripheral arterial embolisms). This brought new absolute totals to 65 PE (35.3%), 3 "other venous thromboembolic events" (1.6%) and 7 arterial thrombotic events (3.8%). It should be noted that of the 65 PE, 19 were limited to subsegmental arteries (29% of PE, or roughly 10% of all events). Crude cumulative composite outcome of venous and arterial events was 57%, or 49% when adjusting for competing risk of death. Authors did note that 17 patients entered the study already on long-term therapeutic anticoagulation (although the exact drug was not specified), and of these, 3 patients developed PE. They also noted that diagnoses were made using CT and ultrasound on basis of suspicion, with no screening. However, CT pulmonary angiogram was used more liberally to investigate patients who were not weaning off the ventilator, especially after the results of the initial study were published [35].

Another retrospective study from the Netherlands included 198 patients (74 in ICU, 124 on a medical ward) admitted to the Amsterdam University Medical Centres [36,37]. Patients were classified as ward patients if they remained stable enough to be on the medical ward, or ICU patients if they went to ICU at any point during their clinical course. All ICU patients required mechanical ventilation in this study. All ICU patients were given thrombosis prophylaxis at standard or double doses. The primary outcome, which included distal or proximal DVT, PE, or venous thrombus in another site, occurred in 33 patients (17%) with an additional patient developing an extensive thrombophlebitis requiring therapeutic anticoagulation. Cumulative incidence calculated using a competing risk model was 15% at 7 days and 34% at 14 days. When considering only symptomatic VTE, the cumulative incidence was 11% at 7 days and 23% at 14 days. The incidence of VTE was drastically different when comparing ICU vs ward patients (39% versus 3.2%). In this study, patients were investigated for thrombotic events based on clinical suspicion, but also were screened at regular intervals.

A third study included COVID-19 patients admitted for ARDS in France included 150 patients admitted to four ICUs at two centres of a tertiary care hospital and compared them to a historical database of patients admitted for ARDS from bacterial and other viral sources using propensity score matching [38]. Primary endpoint was any venous or arterial thrombotic event, and secondary endpoint was to compare the primary endpoints, but also to assess thrombosis of renal replacement therapy (RRT) machines and median lifespan of the machines, ECMO oxygenator coagulation, along with assessing for hemorrhagic complications and coagulation parameters. Out of the 150 patients initially enrolled, there were 25 (16.7%) documented PE and 3 (2%) DVT. After matching, COVID-19 ARDS patients had statistically significant higher rates of PE (11.7% versus 2.1%). There were also higher rates of RRT related thrombotic events. However, other venous and arterial thrombotic events, as well as bleeding, were not significantly different. None of the COVID-19 patients had overt DIC (per ISTH criteria), and only 22 met criteria for Sepsis-Induced Coagulopathy (SIC) as per ISTH Criteria [39]. D-dimer, fibrinogen, Factor V, Factor VIII, vWF activity and antigen were elevated. Furthermore, lupus anticoagulant (LA) was positive in 50/57 of patients tested (87.7%).

The results of this study showed an elevated risk of pulmonary embolism in patients with COVID-19 induced ARDS compared to a population of patients with ARDS from other causes. This study may have underestimated the rate of VTE, given many of the enrolled patients were still intubated at the time the data was reported. This study also demonstrates that the risk of VTE is higher despite the use of guideline-recommended thromboprophylaxis. Furthermore, the coagulopathy seen in COVID-19 was not related to a true DIC, nor was there a high rate of SIC. It could mean that the coagulopathy is due to a different mechanism. The role of antiphospholipid antibodies also remains unclear.

A fourth study including 26 COVID-19 patients admitted to the ICU reported the occurrence of VTE in 69% of patients, using routine ultrasound screening despite the use of prophylactic or therapeutic anticoagulation [40]. Two additional studies from the United Kingdom and China reported VTE in 9% and 25% of patients, respectively

[41,42].

The largest study included 388 patients (362 closed cases) 61 of whom were admitted to the ICU in Milan, Italy [25]. The median duration of hospitalization was 10 days. This study reported thromboembolic events in 7.7% of closed cases with a cumulative rate of 21%. The incidence was higher for patients admitted to the ICU (proportion 16.7% versus 6.4%; cumulative rate 27.6% versus 6.6%). The authors did note that half of the thromboembolic events were diagnosed within 24 h of hospital admission, raising speculation that thrombosis may be either an early complication of COVID-19 or a determinant of further deterioration.

A study from a tertiary care hospital in France evaluated 106 confirmed COVID-19 patients for presence of PE using CTPA. Of the 106 patients, 32 (30%) were found to have PE present on CTPA, 5 of which were in subsegmental arteries only. Patients with PE tended to have higher D-dimer than those who were negative [43].

Another French study analyzed data of 280 COVID-19 patients admitted between March 15 and April 14 [44]. Ultimately, 100 of these patients had contrast CT pulmonary angiography to investigate for presence of PE. Of the 100 patients scanned, 23 (23%) were positive for PE. Authors noted patients with PE were more likely to be mechanically ventilated and tended to have their CT scan performed with a longer delay after initial symptom onset. Although not a direct comparison, this finding may contradict the findings from Lodigiani et al. [25]

While all the previous studies included a significant proportion of patients admitted to an intensive care unit, a recent study conducted in Northern Italy evaluated a group of 388 patients admitted to a non-ICU ward. In this study no patient was found to have a DVT, including 64 patients who had routine lower extremity ultrasound screening. The authors did not comment on whether any of these patients developed PE [45].

Overall, these studies including 1765 patients reported the occurrence of VTE in approximately 20% of patients but with cumulative incidences up to 49% during hospitalization. There were significant differences in screening strategies and definition of outcomes (Table 2). Given the discrepant findings in the reported studies, a post-hoc meta-analysis was conducted (Table 3) and the results suggested that, a) the proportion of VTE is much higher in studies including mostly patients admitted to an intensive care unit and, b) the estimates have a high statistical heterogeneity and there may be a risk for publication bias as suggested by a funnel plot analysis.

3.4.2. Arterial thrombosis

Regarding cerebrovascular disease a case series from New York described 5 patients with SARS-CoV-2, all < 50 years old, who presented with acute ischemic stroke. Only one had a history of prior stroke [46]. The data from observational studies is summarized in Table 4. A retrospective study of 214 COVID-19 patients admitted to hospital was conducted in Wuhan. Six (2.8%) patients had acute stroke, 5 of them classified as having “severe” disease. Although no definition was provided, patients with “severe” disease had higher frequency of co-morbidities including hypertension and were older on average [47]. Reports from other groups are very similar with a reported occurrence of stroke between 2.7% and 3.8% of patients [25,34,35,38,42]. Overall, all studies included 973 patients with a pooled proportion (random effects model) of 3.5% (95% CI 2.4 to 4.8) with no statistical heterogeneity.

A case report highlighted the possibility of cardiovascular arterial thrombosis in a patient presenting with ST segment myocardial infarction in whom coronary angiography and optical coherence tomography revealed the presence of thrombus without atheroma, and therefore, it was hypothesized that in-situ thrombosis was responsible for their formationCOVID-19 [48]. Findings of cardiovascular thrombosis have been seen in other studies as well [25].

3.4.3. Diagnosis of venous thromboembolic disease

Diagnosis of thromboembolic disease can be difficult in patients with SARS-CoV 2 infection. Patients with severe disease requiring hospitalization often have elevated D-Dimer levels since it is considered as an acute phase reactant, thus limiting its utility as a screen for venous thromboembolism [9] because, although it has a very high sensitivity for thrombotic disease, its specificity is poor [49]. A retrospective study reported the clinical and imaging characteristics of 25 patients with COVID-19 pneumonia suspected of PE: 10 found to have an objectively confirmed PE, and 15 with negative imaging. The median D-dimer level was 11.07 μg/ml (IQR, 7.12–21.66) in the PE patients versus 2.44 μg/ml (IQR, 1.68–8.34) in PE negative patients ($p < 0.05$). Authors suggested that in COVID-19 patients with rising D-dimer level, CTPA can be applied to detect PE and monitor patients with COVID-19 [50]. Notwithstanding this report, given the limited data to date a good diagnostic algorithm not relying on D-Dimer becomes important. This presents a new challenge, as hospitals try to find creative ways to isolate patients with COVID-19, and prevent aerosol generating procedures and tests. Furthermore, less direct contact of patients with healthcare workers can help to prevent the spread of infection and can help to preserve personal protective equipment (PPE) supplies.

Zuckier et al. proposed a diagnostic algorithm to try to balance these seemingly competing factors [51]. They suggest that nuclear medicine ventilation perfusion imaging (VQ Scans) may be of limited utility for several reasons including the fact that many hospitalized patients with COVID-19 have pulmonary abnormalities on chest x-ray, which would reduce the accuracy of VQ scanning. Furthermore, the ventilation portion of the exam may cause aerosol generation, which may put healthcare workers at increased risk of contracting SARS-CoV-2. The exact algorithm states that if no pulmonary abnormalities are present on chest X-ray, a VQ scan could be performed using the perfusion portion only. If there are no perfusion defects, pulmonary embolism can be excluded. If there are perfusion abnormalities, the patient should be evaluated for consideration of CTPA. CTPA should be performed if there are no contraindications. If CTPA is contraindicated, ultrasound of the leg veins can be performed if symptoms of DVT are present. If there are no DVT symptoms present and CTPA is contraindicated, the full VQ scan can be performed. If the full VQ scan is the only option, healthcare workers should take appropriate precautions and use PPE as directed by local health authorities. The validity and practicality of this algorithm is yet to be determined. The National Institute for Public Health of the Netherlands recently published guidance on diagnosis and management of thrombosis in COVID-19. In this position paper, the authors suggest a baseline CT chest for all patients suspected of COVID-19 who are admitted to hospital. They suggest CTPA for diagnosis when PE is suspected. They also suggest sequential monitoring of D-dimer levels, and investigation for DVT or PE if D-dimer rises above 2000–4000 μg/L, especially if there is clinical suspicion for thrombosis [49].

3.5. Treatment of thrombosis in COVID-19

3.5.1. Effect of heparin on mortality

Given the potential severity of the disease in hospitalized patients, as well as the risk of thrombosis, current guidelines recommend using pharmacological DVT prophylaxis in all patients. However, these recommendations are based on general thromboprophylaxis, and are not specific to COVID-19 [5,6]. There is no general agreement on the optimal dosing in this setting, and various papers have suggested heterogeneous protocols.

A retrospective review from Wuhan, China evaluated the effect of both UFH and LMWH on mortality in severe COVID-19 patients [52]. The authors compared severe COVID-19 patients with another subset of patients admitted to ICU with non-COVID-19 pneumonia. Severe COVID-19 was defined as meeting one of the following criteria: respiratory rate ≥ 30, arterial oxygen saturation ≤ 93% at rest, or a P/F ratio ≤ 300 mmHg. A total of 449 severe COVID-19 patients were

Table 2
Frequency of venous thromboembolic complications in COVID-19 patients.

Study	Proportion[a]	Cumulative incidence	Median follow-up	Comments	DVT prophylaxis
Leonard-Lorant et al. [43]	PE only 32/106 (30%)	NR	NR	D-dimer cutoff of 2660 μg/L had 100% sensitivity for PE. 24/32 (75%) PE positive patients were in ICU.	Anticoagulant not specified. In PE positive group, 25/32 (78%) were on prophylactic doses and 2/32 (6%) were on therapeutic doses.
Grillet et al. [44]	PE only 23/100 (23%)	NR	NR	Ward: 6/61 (9.8%) ICU: 17/39 (43.6%)	NR
Poissy et al. [33]	PE only 22/107 (20.6%)	20.4% Calculated at ICU day 15	6 days	ICU only	20 out of the 22 PE patients were on prophylactic LMWH or UFH, but exact agents not specified.
Klok et al. [34,35]	68/184 (37%)	57%, or 49% adjusted for competing risk of death	14 days	ICU patients only. 19 PE were limited to subsegmental arteries. 65/68 venous events were PE (95.6%).	Varied by centre. Nadroparin at doses of 2850 IU OD, 5700 IU OD, or 5700 IU BID were used (see full text).
Middeldorp et al. [36,37]	33/198 (17%)	15% at 7 days 34% at 14 days	5 days	Ward: 4/123 (3.3%) ICU: 35/75 (47%) 11 (5.4%) clots detected on screening 11/33 events were PE (33%)	ICU patients from April 3rd onwards received nadroparin 2850 IU BID if weight < 100 kg, and 5700 IU BID if weight > 100 kg. Ward patients had half this dose.
Helms et al. [38]	27/150 (18%)	NR	NR	ICU patients with ARDS 25/27 events were PE (92.5%)	LMWH (exact agent not specified) 4000 Units per day or UFH 5–8 U/kg/h
Llitjos et al. [40]	DVT: 18/26 (69%) PE: 6/26 (23%)	NR	NR	ICU patients. Systematic ultrasound screening.	LMWH and UFH were used (exact agents not specified) Prophylactic dose in 8/26 (31%) Therapeutic dose in 18/26 (69%)
Lodigiani et al. [25]	16/362 (4.4%)	21% (time not reported)	10 days	ICU 4/48(8.3%) Ward 12/314 (3.8%)	100% of ICU patients 75% of ward patients Exact regimen not specified
Thomas et al. [42]	6/63 (9%)	27%	8 days	ICU patients	All patients assessed for use of prophylaxis with weight-adjusted Dalteparin. Exact number of patients receiving prophylaxis not mentioned.
Cui et al. [41]	20/81 (25%)	NR	NR	ICU patients	None
Cattaneo et al. [45]	DVT only 0/388 (0%)	NR	NR	Non-ICU Ward 64 patients had screening ultrasound. All Negative.	Enoxaparin 40 mg daily

NR, not reported, DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; LMWH low molecular weight heparin; UFH, unfractionated heparin.
[a] Proportions reflect number of patients, not individual thrombotic events.

evaluated in the study. All COVID-19 patients received antivirals and supportive care. 99 (22%) of these patients received either UFH (10,000–15,000 units/day) or LMWH (Enoxaparin 40–60 mg/day). There was no difference in mortality in heparin users vs non-users. However, in a subset of COVID-19 patients who had D-Dimer levels > 3.0 μg/mL (six-fold the upper limit of normal), there was a statistically significant decrease in mortality in heparin users vs non-users (32.8% vs 52.4%, p = 0.017). Furthermore, in another subset of patients with Sepsis Induced Coagulopathy (SIC) Score ≥ 4, there was a significant reduction in mortality between heparin users and non-users (40.0% vs 64.2%, p = 0.029). There was no difference in mortality between non-COVID-19 heparin users and non-users, even when stratified by D-Dimer levels and SIC score. However, other aspects of the patients' treatment were not discussed, and it is unclear if other treatments (antivirals, antibiotics, ventilator settings, etc.) could have contributed to differences in mortality. The authors also correctly point out that this study was done in Wuhan at a time when medical resources were strained and thus the mortality rate may not be representative of that in other parts of the world. Lastly, the dosing of UFH and LMWH was not controlled for. This study does not evaluate whether COVID-19 patients with elevated D-Dimer or SIC score would benefit from a different dose of UFH or LMWH compared to generally accepted DVT prophylaxis doses. It does not seem that patients routinely received thromboprophylaxis in this study, and it is not clear if mortality would be different had all patients received guideline-recommended prophylaxis. Other studies [25,34,36,38,42] report using both standard and increased prophylactic doses of LMWH, however no information is available on the risk of VTE between these groups.

Table 3
Meta-analysis estimates of the proportion of venous thromboembolic events in COVID-19 patients.

	Fixed effects model		Random effects model		
	Percent	95% CI	Percent	95% CI	Higgins' I^2
All studies [25,33,35,36,38,40–45]	12.2	10.7 to 13.8	21.9	11.2 to 34.9	97.3%
All studies excluding extreme outliers [25,33,35,36,38,41–44]	16.8	14.9 to 18.9	19.5	11.9 to 28.4	93.2%
Studies including over 75% ICU patients [33,35,38,40–43]	27	23.8 to 30.4	31.27	19.1 to 44.7	92.9%
Studies including < 75% ICU patients [25,36,44,45]	4.9	3.7 to 6.5	8.6	1.3 to 21.5	97.1%

ICU, intensive care unit.

Table 4
Frequency of cerebrovascular disease in COVID-19 patients.

Study	Proportion[a]	Median follow-up	Comments	DVT prophylaxis
Mao et al. [47]	6/214 (2.8%)	NR	All admitted patients	Not reported
Klok et al. [34,35]	7/184 (3.8%)	14 days	ICU patients only	Varied by centre. Nadroparin at doses of 2850 IU OD, 5700 IU OD, or 5700 IU BID were used (see full text).
Helms et al. [38]	4/150 (2.7%)	NR	ICU patients with ARDS only	LMWH (exact agent not specified) 4000 Units per day or UFH 5–8 U/kg/h
Lodigiani et al. [25]	13/362 (3.6%)	10 days	Patients admitted to ICU: 4/48 (8.3%)	100% of ICU patients
			Patients admitted to non-ICU Ward: 9/314 (2.9%)	75% of ward patients
				Exact regimen not specified
Thomas et al. [42]	2/63 (3.2%)	8 days	ICU patients only	All patients assessed for use of prophylaxis with weight-adjusted Dalteparin. Exact number of patients receiving prophylaxis not reported.

NR, not reported; ICU, intensive care unit; LMWH low molecular weight heparin; UFH, unfractionated heparin.
[a] Proportions reflect number of patients, not individual thrombotic events.

However, a small series of 26 patients admitted to the ICU reported a higher frequency of VTE in patients receiving prophylactic anticoagulation compared to those receiving therapeutic anticoagulation (100% vs 56%) although the size of the sample prevents drawing definitive conclusions [40].

An observational study from New York aimed to better clarify the effect of full therapeutic dose anticoagulation on patients with COVID-19. It included 2773 hospitalized patients, of which 786 (23%) were on therapeutic AC. Unfortunately, authors could not capture data on the type or dose of anticoagulants used, nor the indication for AC. The results interestingly demonstrated a stark difference between patients on mechanical ventilation and those who were not. For those mechanically ventilated (N = 395), in-hospital mortality was 29.1% with a median survival of 21 days for those receiving AC, compared to 62.7% with a median survival of 9 days for those not receiving AC. In contrast, the general population of patients receiving AC showed an in-hospital mortality of 22.5% with a median survival of 21 days, compared to 22.8% and 14 days in those not receiving AC [53]. In general, this study, although limited by its observational nature and lack of patient data, provides an interesting insight into the potential of therapeutic AC in the treatment of COVID-19.

3.5.2. Tissue plasminogen activator (tPA) in COVID-19 ARDS

Evidence of microthrombi and coagulopathy in critically ill COVID-19 patients prompted the possibility of tissue plasminogen activator (tPA) as a potential treatment. A small case series of 3 mechanically ventilated patients admitted to an ICU in the United States reported the use of systemic tPA (25 mg over 2 h followed by another 25 mg over the subsequent 22 h. All three patients experienced improvement in their ventilatory parameters but the effect of this intervention on long term outcomes in unknown. A second case series assessed the effect of aerosolized freeze-dried plasminogen in moderately, severely or critically ill COVID-19 patients. The study reported significant improvement in oxygenation and ventilatory parameters [54]. Current studies are being conducted to evaluate these interventions (NCT04356833, NCT04357730).

3.5.3. Use of direct oral anticoagulants (DOACs)

Although data is sparse, a study from Italy followed 12 patients on DOACs before and during hospital admission for COVID-19. All patients received either levofloxacin or azithromycin with hydroxychloroquine and anti-viral drugs including lopinavir/ritonavir or darunavir/ritonavir and had significant elevations in DOAC plasma levels likely mediated by the inhibition of P-glycoprotein or cytochrome P450 metabolic pathways from the antiviral medications [55].

4. Discussion

In the present review we identified a reported overall VTE frequency of approximately 20% of patients and of stroke of approximately 3%. Cumulative incidences were reported as high as 49% at varying time periods. There was an unusually high frequency of PE and the frequency of VTE was significantly higher in severely ill patients admitted to the ICU, compared to patients admitted to regular wards. Most importantly, many patients developed thrombotic episodes despite the use of prophylactic anticoagulation, either at standard or higher doses. For this reason, many groups have advised using higher than usual anticoagulant prophylactic doses, however it is unknown if this strategy is appropriate or not and several studies are currently ongoing (NCT04345848, NCT04359277, NCT04344756, NCT04360824, NCT04354155, NCT04359212, NCT04362085).

Data evaluating when patients are most at risk of thrombosis is lacking. While some studies seem to suggest thrombosis may be an early finding [25], others have found thrombotic events occurring even after patients are discharged from hospital [48]. This highlights a need for more research, and whether these events can be more accurately predicted by biomarkers, such as D-dimer. Several studies suggest substantial coagulation activation with severe COVID-19 infection likely related to sustained inflammatory response due to cytokine release induced by virus invasion. Pulmonary vasculature thrombosis is likely to be at least in part a result of the severe hypoxia for hypoxia is a profound stimulant of coagulation [56]. The most prominent coagulation marker is the marked and dynamic elevation of D-dimer levels that has been consistently reported in those studies, potentially representing a prognostic indicator for severity and mortality. The high D-dimer probably indicates a severe inflammatory response accompanied by a secondary hypercoagulable state. In fact, D-dimer is also a marker of pulmonary fibrin deposition typical of several lung diseases, notably ARDS [57], commonly seen in severe COVID-19. This is supported by data showing that the time course of D-dimer elevation mirrors that of other inflammatory markers including ferritin, interleukin 6, troponin I and lactate dehydrogenase [14]. Moreover, DIC as defined by the ISTH score demonstrated to be a significant finding among non-survivors indicating that it is an adverse prognostic marker [9]. Of note, platelet count seems to be only mildly reduced in general, and prothrombin time showed persistent elevation as opposed to the expected reduced fibrinogen levels seen in DIC with sepsis. However, those studies have methodological limitations mainly related to sample size and short incomplete follow up. Additionally, it has been demonstrated that D-dimer reagents are not interchangeable when assessing their use for clinical diagnosis of VTE [58,59]. Currently, it is not known whether this would be a limitation for their use in prognostic models in COVID-

19 patients. Properly conducted prospective studies are needed in this area.

The significant and overwhelming inflammatory response in patients with severe COVID-19 infection may increase the likelihood of thromboembolic disease and in turn explain the high frequency of VTE, particularly in patients admitted to the ICU. However, it is unclear if COVID-19 is more likely to cause venous or arterial thrombosis than other conditions. It has been previously reported that patients with severe sepsis (non-COVID-19) or septic shock have a very high incidence of VTE of up to 37% despite the use of guideline-recommended thromboprophylaxis [60], and it is known that general ICU patients frequently fail VTE prophylaxis (4.45%, 7.14%, 7.53% at 7, 14 and 21 days, respectively) [61]. Inferences on the risk of VTE in patients with COVID-19 need to be interpreted in this context, keeping in mind that severe sepsis causes a similar picture with higher rates of VTE despite adequate VTE prophylaxis although some evidence suggests that indeed COVID-19 has a higher thrombotic risk compared to patients admitted to the ICU for other causes [38]. An important point is the fact that there is no information regarding the risk of thrombosis after hospital discharge. This topic needs to be urgently addressed.

An emerging hypothesis worth considering is the possibility that the pathophysiology of the pulmonary thrombotic events in COVID-19 may not be embolic at all which could have major implications for treatment. Support for this hypothesis comes from both pathology and clinical data. A review of 10 autopsies of COVID-19 patients (5 men, 5 women) found evidence of microthrombi in lung tissue, raising the speculation that in-situ pulmonary thrombosis may be the culprit pathophysiological mechanism [62]. From a clinical perspective, several studies have found that a disproportionate high number of venous clotting events are pulmonary thrombi [34–36,38] without an associated increase in deep vein thrombosis [45]. Given this data, we and other authors question whether the high number of PE are due to embolic events, or rather, in-situ pulmonary thrombosis [45] and pose the question of whether focusing on anticoagulation is the right approach to decrease the thrombotic risk in COVID-19 patients as treating all patients with higher doses of anticoagulants without a clear indication may be more harmful. It seems that thrombosis, be it macro or microvascular, is the result of the severe inflammatory response induced by. SARS-CoV-2 with its subsequent endothelial dysfunction and procoagulant environment and thus targeting inflammation in conjunction with rational anticoagulant management might be a preferable approach.

For this reason, some groups have proposed a staging classification that considers both clinical and laboratory criteria and suggest potential treatments for each stage [63]. In short, they suggest that in stage 1, where patients are either at home or hospitalized on a non-ICU general medical ward, patients may have pulmonary micro-thrombi and require prophylactic vs therapeutic doses of heparin. In stage 2, patients are sicker, requiring ICU admission, and have evidence of overt thrombotic events. In this stage, therapeutic dose anticoagulation is required, and the potential exists for more experimental treatments, such as complement system inhibition. In the third and final stage, patients have deteriorated to the point of overt DIC with potential treatments such as tPA in addition to the therapeutic heparin. Although this classification has yet to be validated or proven, it does provide an intriguing hypothesis to the underlying pathophysiology and potential for future research.

In summary, a number of pressing issues were identified by this review, including defining the true incidence of VTE in COVID patients, developing algorithms to identify those susceptible to develop thrombosis and/or severe disease, determining the role of biomarkers such as D-dimer and/or scoring systems to stratify patients' risk, designing adequate and feasible diagnostic protocols for PE and establishing the optimal thromboprophylaxis strategy, either with standard, increased or therapeutic doses, given the known risk of hemorrhage associated with anticoagulants. Finally, and most importantly, there is an urgent need to develop standard clinical definitions, common data elements, and standard reporting criteria in order to facilitate future research.

Declaration of competing interest

Authors declare no conflicts.

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Contributions

FA-A, SC, AL-L, designed the study, extracted data and wrote the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.05.039.

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