

# Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis

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## ABSTRACT

**Background** The prevalence of venous thromboembolic event (VTE) and arterial thromboembolic event (ATE) thromboembolic events in patients with COVID-19 remains largely unknown.

**Methods** In this meta-analysis, we systematically searched for observational studies describing the prevalence of VTE and ATE in COVID-19 up to 30 September 2020.

**Results** We analysed findings from 102 studies (64 503 patients). The frequency of COVID-19-related VTE was 14.7% (95% CI 12.1% to 17.6%,  $I^2=94%$ ; 56 studies; 16 507 patients). The overall prevalence rates of pulmonary embolism (PE) and leg deep vein thrombosis were 7.8% (95% CI 6.2% to 9.4%,  $I^2=94%$ ; 66 studies; 23 117 patients) and 11.2% (95% CI 8.4% to 14.3%,  $I^2=95%$ ; 48 studies; 13 824 patients), respectively. Few were isolated subsegmental PE. The VTE prevalence was significantly higher in intensive care unit (ICU) (23.2%, 95% CI 17.5% to 29.6%,  $I^2=92%$ , vs 9.0%, 95% CI 6.9% to 11.4%,  $I^2=95%$ ;  $p_{\text{interaction}} < 0.0001$ ) and in series systematically screening patients compared with series testing symptomatic patients (25.2% vs 12.7%,  $p_{\text{interaction}} = 0.04$ ). The frequency rates of overall ATE, acute coronary syndrome, stroke and other ATE were 3.9% (95% CI 2.0% to 3.0%,  $I^2=96%$ ; 16 studies; 7939 patients), 1.6% (95% CI 1.0% to 2.2%,  $I^2=93%$ ; 27 studies; 40 597 patients) and 0.9% (95% CI 0.5% to 1.5%,  $I^2=84%$ ; 17 studies; 20 139 patients), respectively. Metaregression and subgroup analyses failed to explain heterogeneity of overall ATE. High heterogeneity limited the value of estimates.

**Conclusions** Patients admitted in the ICU for severe COVID-19 had a high risk of VTE. Conversely, further studies are needed to determine the specific effects of COVID-19 on the risk of ATE or VTE in less severe forms of the disease.

## INTRODUCTION

COVID-19 is a viral respiratory illness caused by SARS-CoV-2. In severe cases, COVID-19 is characterised by cytokine outburst and hyperinflammation, platelet activation, endothelial dysfunction and sepsis-related coagulopathy.<sup>1</sup> Consistently, high levels of D-dimers were repeatedly shown to be associated with the need for intensive care unit (ICU) admission and mortality among patients with COVID-19.<sup>2</sup> While initial anecdotal reports described cases of pulmonary embolism (PE) diagnosed concomitantly with COVID-19,<sup>3</sup> more

## Key messages

### What is the key question?

- Are arterial and venous thromboembolic events common in patients with COVID-19, and what condition may modify their prevalence?

### What is the bottom line?

- Our results suggested that venous and, in to a lesser extent, arterial thromboembolism, are common in patients with COVID-19 admitted in the intensive care unit, despite thromboprophylaxis. The systematic screening of venous thromboembolism may be relevant.

### Why read on?

- This is the first systematic evaluation of existing evidence regarding thrombotic manifestations of COVID-19, summarising the current evidence on a novel spectrum of this viral disease.

recent observational studies suggested that venous thromboembolic events (VTEs) are common among patients with COVID-19 hospitalised in the ICU, thrombosis prevalence ranging from 0%<sup>4</sup> to 69%.<sup>5</sup> Few series also suggested an elevated incidence of arterial thromboembolic events (ATEs).<sup>6,7</sup> Importantly, however, these prevalence estimates have been largely inconstant with a high heterogeneity across studies and are subjected to several biases. Moreover, many series also reported a low prevalence of deep vein thrombosis (DVT),<sup>4</sup> questioning the peculiar mechanism responsible for pulmonary vessel occlusions.

While international experts recently recommended an early therapeutic anticoagulation for these patients despite the increased risk of bleeding and previous negative trials of endogenous anticoagulants in sepsis,<sup>8,9</sup> relevant estimates of the occurrence of ATE and VTE are lacking to inform on the best therapeutic approach in these patients. Therefore, the present meta-analysis aimed to determine the prevalence of VTE and ATE in patients with COVID-19.

## MATERIALS AND METHODS

This systematic review and meta-analysis (<http://www.crd.york.ac.uk/PROSPERO>, CRD42020184252) was conducted in accordance with the *Cochrane Handbook for Systematic Reviews*



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of *Interventions*<sup>10</sup> and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>11</sup>

### Search strategy

A literature search was performed to identify all published studies reporting thromboembolic events in COVID-19. MEDLINE, Embase and Google Scholar were searched between 1 January 2020 and 30 September 2020 using the keywords “coronavirus”, “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2”, “novel coronavirus”, “nCoV”, “2019-nCoV”, and “COVID-19” and “thrombosis”, “stroke”, “myocardial infarction”, “acute coronary syndrome”, “pulmonary embolism” and “venous thromboembolism” (see appendix). The websites of major journals were also searched, including the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, *Lancet Haematology*, *British Medical Journal*, *Journal of the American College of Cardiology*, *Circulation*, *Journal of Thrombosis and Haemostasis*, *Thrombosis and Haemostasis* and *Thrombosis Research*. Bibliographies of each included study, as well as any review article, systematic review, meta-analysis or text found were also searched for additional papers that may contain further studies. Given that preprint papers in databases such as bioRxiv and medRxiv were not peer-reviewed, we did not include papers found in such databases in our analysis to avoid any potential misinformation being disseminated. There was no restriction on the language and type of publication.

### Study selection

The inclusion criteria for studies were the following: (1) cohort studies of >10 patients, (2) patients with COVID-19 (positive reverse transcription PCR (RT-PCR)) or positive CT scan in patients with suggestive gestalt and (3) available rate of objectively documented ATE or VTE as defined by investigators. Moreover, publications specific to the paediatric population were excluded.

The titles and abstracts of all articles were independently reviewed by two authors (BKT and J-CL). If pertinent, each reviewer independently retrieved and explored complete articles to make a final decision about their inclusion in the meta-analysis. Disagreements were resolved by consensus or by consulting a third reviewer (SM). Throughout this process, the reviewers were blinded to authors' names, journal and year of publication of the papers. If studies that had been reported in multiple papers were identified, the analysis was limited to the largest cohort unless the necessary data had appeared only in another paper. A log of reasons for rejection of citations identified from the searches was kept.

### Outcomes

The main outcomes were the rate of distal (located below the knee) and proximal (involving popliteal, femoral, iliac vein and inferior vena cava) DVT, VTE (distal and proximal DVT and PE) and the rate of ATE (myocardial infarction, stroke, limb and visceral arterial ischaemia).

### Assessment of methodological quality

The methodological quality of the selected studies was systematically evaluated using the Methodological Index for Non-randomised Studies (MINORS), which contains six items for non-comparative studies.<sup>12</sup>

### Data extraction

Two reviewers (BKT and J-CL) independently extracted study design; the study country; patient characteristics, including the proportion of patients hospitalised in the ICU; the method used to diagnose COVID-19 and VTE; the follow-up duration, whether symptomatic testing versus asymptomatic screening was performed; and the proportion of patients receiving anticoagulants.

### Statistical analysis

We constructed a random-effects (Mantel-Haenszel) model to obtain a summary estimate and 95% CI for the prevalence of VTE and ATE using arcsine transformation. These data were combined by using an approximation to the inverse variance approach, effectively weighting each study according to its sample size. Arcsine transformation was used to stabilise the variance.<sup>13</sup>  $I^2$  statistic for heterogeneity was used to assess between study heterogeneity. To investigate sources of heterogeneity in the main analysis, if any, we planned a priori subgroup analyses for relevant categorical variables (single centre vs multicentre, consecutive vs non-consecutive series, retrospective vs prospective, systematic assessment of thrombosis vs symptomatic testing, a majority of included patients being hospitalised within the ICU or not), as well as metaregression for continuous variables (study size, the MINORS score, proportion of male sex,<sup>14</sup> mean lymphocyte count<sup>15</sup> and D-dimer value,<sup>15</sup> proportion of patients hospitalised in the ICU,<sup>14</sup> proportion of patients receiving anti-coagulants). Metaregression was not performed if the number of studies was  $\leq 10$  to avoid overfitting using linear weighted random/mixed-effects model (rma function, metafor package).<sup>16</sup>

Publication bias was assessed visually using funnel plots. We assumed that the effect of publication bias should be minor if the plot of the magnitude of effect size in each study versus its precision estimate (ie, SE) shows a roughly symmetrical funnel shape. We also formally tested the presence of publication bias using the SE-based and study size-based funnel plot and related asymmetry tests. All analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria).

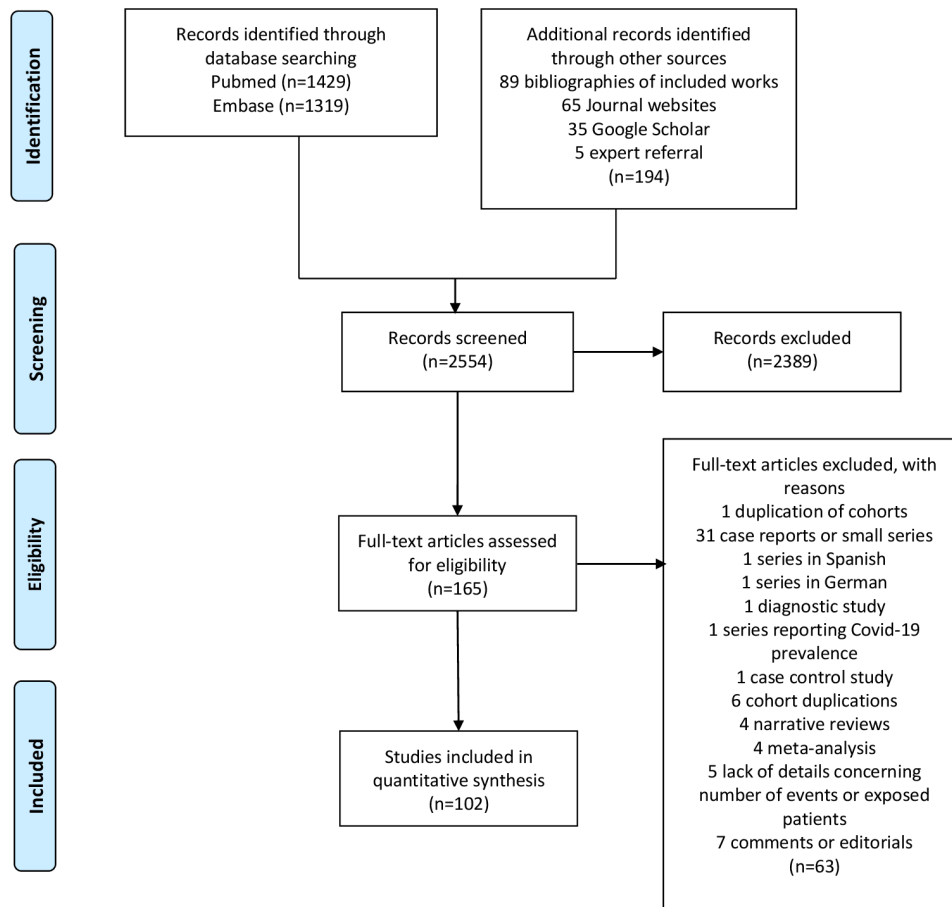
## RESULTS

### Literature search and agreement

A total of 2554 articles were retrieved by the search terms. After reviewing titles and abstracts, 165 articles were selected for the full-text eligibility. Finally, 102 studies (64503 patients) were included (figure 1).

### Study characteristics

Among included studies, 81 series assessed COVID-19-related VTE and 20 studies reported ATE. The characteristics of the included studies are described in online supplemental table S1. The patient number varied from 12 to 12630. Twenty-three (23%) studies were prospective; 74 (73%) included consecutive patients. Thirty-four (33%) studies were conducted in ICU. Two studies used electronic medical records to identify thrombotic events.<sup>17 18</sup> Eligible studies ranged in size from 12 to 12630 patients, while mean follow-up duration ranged from 8 to 86 days. The presence of DVT and PE was confirmed with ultrasonography and CT scan, respectively, although PE was confirmed using echocardiography in patients with high suspicion in two studies.<sup>7 17</sup> Thirty-seven (36%) studies, mainly letters, did not report the method of VTE detection. The all-cause mortality varied from 0% to 64%. The rate of patients receiving pharmacological VTE prophylaxis ranged from 16% to 100%. The



**Figure 1** Study selection.

median MINORS quality score was 7 (range 1–12) (online supplemental table S2).

### Venous thromboembolism

The overall weighted frequency of COVID-19-related VTE was 14.7% (95% CI 12.1% to 17.6%,  $I^2=94\%$ ; 56 studies; 16 507 patients; [figure 2](#)).<sup>4 5 15 17–68</sup> The visual inspection of funnel plot and the Egger's regression test ( $p<0.0001$ ) were in favour of publication bias (online supplemental figure S1). VTE included PE (7.8%, 95% CI 6.2% to 9.4%,  $I^2=94\%$ ; 66 studies; 23 117 patients; online supplemental figure S2)<sup>4–7 15 17–19 21–25 29 29–31 33 34 36–52 55 56 58 59 61 63–67 69–88</sup>

and leg DVT (11.2%, 95% CI 8.4% to 14.3%;  $I^2=95\%$ ; 48 studies; 13 824 patients; online supplemental figure S3).<sup>4 7 15 17 18 22–25 29–31 33 34 36 37 41–45 48–51 55–58 60 61 64 65 67 69 72 85 89–98</sup>

Few PE events resulted from isolated subsegmental PE (1.5%, 95% CI 0.9% to 2.4%;  $I^2=75\%$ ; 22 studies; 1391 patients; online supplemental figure S4),<sup>4 7 17 24 30 34 39 48 51 53 55–57 60 63 64 67 73 76 78 81 99</sup> whereas distal DVT (10.9%, 95% CI 4.8% to 18.9%,  $I^2=97\%$ ; 19 studies; 2421 patients; online supplemental figure S5)<sup>4 19 22 23 30 34 36 38 53 55 57 67 88–90 93 94 97 100</sup>

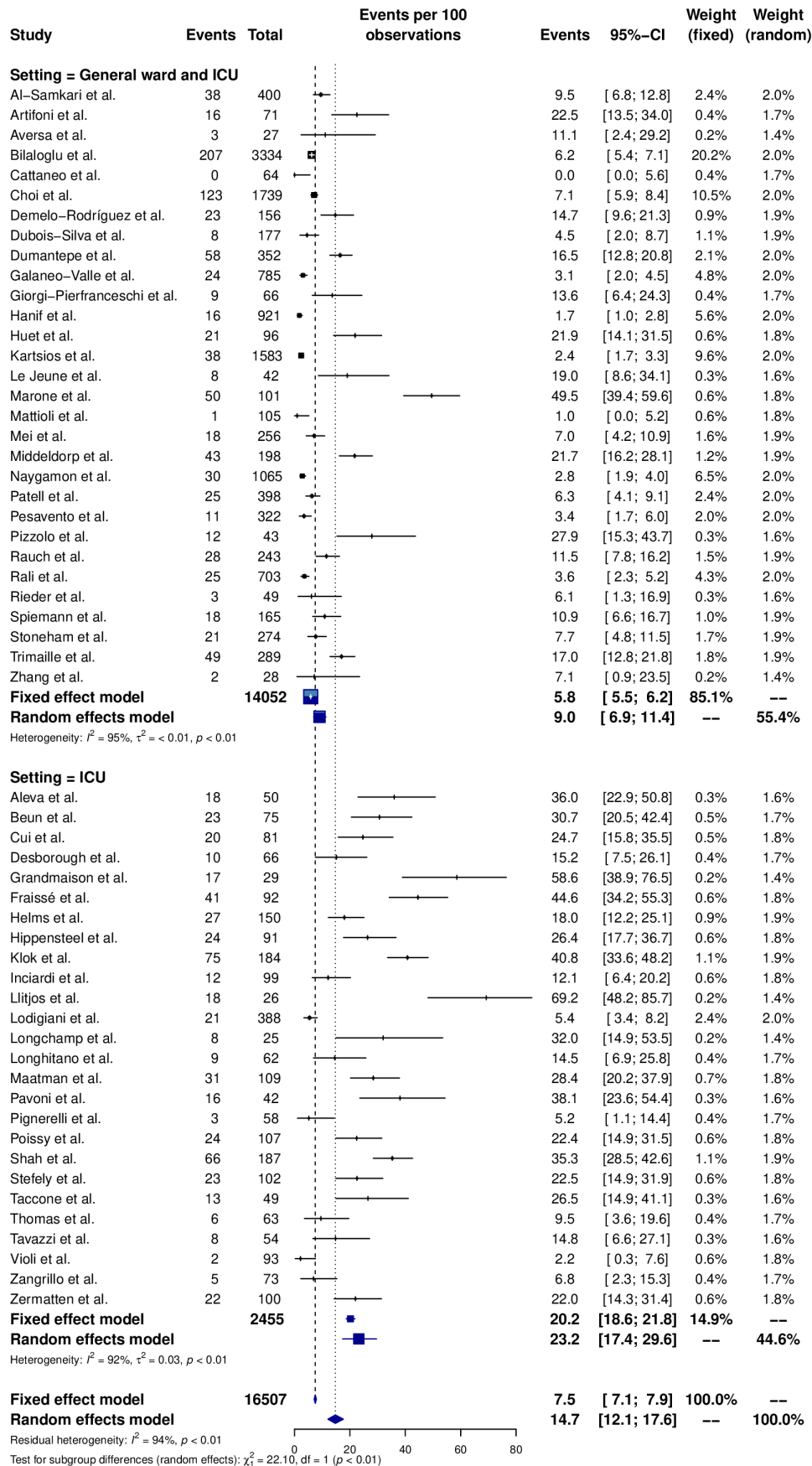
was more frequent than proximal DVT (4.8%, 95% CI 2.8% to 7.2%,  $I^2=89\%$ ; 26 studies; 3735 patients; online supplemental figure S5).<sup>4 17 19 22 23 26 30 34 36 38 40 41 49 53 55–57 59 65 67 88–90 93 94 97 100</sup>

In subgroup analyses, the VTE prevalence was significantly higher in ICU cohorts than cohorts including mixed patients (23.2%, 95% CI 17.4% to 29.6%;  $I^2=92\%$ , vs 9.0%, 95% CI 6.9% to 11.4%;  $I^2=95\%$ ;  $p_{\text{interaction}}<0.0001$ ; [figure 2](#) and [table 1](#)). Post hoc subgroup analyses retrieved similar interactions for PE (13.5%, 95% CI 9.5% to 18.1% vs 5.2%; 95% CI 3.9 to 6.7;  $p_{\text{interaction}}<0.0001$ ; online supplemental figure S2),

DVT (21.1%, 95% CI 13.8% to 29.5% vs 4.7%, 95% CI 2.9 to 6.8;  $p_{\text{interaction}}<0.0001$ ; online supplemental figure S3) and proximal DVT (9.0%, 95% CI 3.5% to 16.6% vs 2.6%, 95% CI 1.2 to 4.5;  $p_{\text{interaction}}<0.0001$ ; online supplemental figure S6). This relation between ICU admission and VTE prevalence was supported by metaregression analyses ([table 2](#) and [figure 3](#)). In addition, the VTE prevalence was higher in multicentric versus monocentric series, in studies using systematic screening versus symptomatic testing ([table 2](#) and online supplemental figure S7), in larger cohorts and in studies with high mean D-dimers values ([table 2](#)). Conversely, the VTE prevalence was not associated with the MINORS score, the proportion of patients receiving anticoagulation or the study design, and proportion of men ([tables 2 and 3](#)). The rate of ICU patients and systematic screening were significantly associated to VTE prevalence in multivariable metaregression ([table 3](#)).

### Arterial thromboembolism

The weighted frequency of ATE was 4.0% (95% CI 2.0% to 6.5%,  $I^2=95\%$ ; 19 studies; 8249 patients),<sup>7 17 18 27 36 39 42 45 47 50 51 53 55 61 65–67 88 101 102</sup> including myocardial infarction/acute coronary syndrome (1.1%, 95% CI 0.2% to 3.0%,  $I^2=96\%$ ; 16 studies; 7939 patients),<sup>7 17 18 39 47 50 51 53 55 61 65 66 88 101–103</sup> ischaemic stroke (1.6%, 95% CI 1.0% to 2.2%,  $I^2=93\%$ ; 27 studies; 40 597 patients)<sup>7 18 27 36 39 42 45 47 50 51 53 55 61 65–67 88 101 102 106</sup> and other ATE (0.9%, 95% CI 0.5% to 1.5%;  $I^2=84\%$ ; 17 studies; 20 139 patients)<sup>7 17 18 27 47 50 51 53 55 61 65–67 88 101 102 106</sup> ([figure 4](#)). The visual inspection of funnel plot and Egger's regression test ( $p=0.008$ ) were in favour of publication bias (online supplemental figure S1). Subgroup analyses (online supplemental table



**Figure 2** Forest plot showing the pooled, weighted frequency of patients with venous thromboembolic events related to COVID-19 according to patient population. ICU, intensive care unit.

**Table 1** Subgroup analysis to explore heterogeneity in estimate of VTE prevalence

	Studies (k)	Patients (n)	Prevalence (%) (95% CI)	I <sup>2</sup> (%)	P value
Approach to VTE diagnosis					0.04
Asymptomatic screening	12	842	25.2 (13.5 to 39.1)	95	
Symptomatic testing only	44	15 665	12.7 (10.1 to 15.4)	96	
Patients in ICU					<0.0001
>70%	26	1686	23.2 (17.4 to 29.6)	92	
≤70%	30	14 052	9.0 (6.9 to 11.4)	95	
Prospective series					0.64
Yes	12	14 653	13.1 (10.4 to 16.1)	96	
No/unknown	44	1828	22.0 (12.9 to 32.7)	96	
Multicentric series					0.10
Yes	12	2808	28.5 (16.2 to 42.6)	98	
No	44	13 673	14.3 (10.6 to 18.5)	94	
Consecutive series					0.42
Yes	14	11 495	15.5 (12.2 to 19.2)	96	
No/unknown	42	4986	12.7 (7.7 to 18.8)	95	

ICU, intensive care unit; VTE, venous thromboembolism.

S3) and metaregression (online supplemental table S4) failed to identify other factor explained heterogeneity.

**DISCUSSION**

The present meta-analysis showed a high prevalence of VTE in patients with COVID-19, especially for those admitted to the ICU. The prevalence of ATE was also substantial, although the low number of studies reporting this outcome among patients with COVID-19 limited precise estimates of the ATE risk according to patients’ characteristics. Taken together, these observations suggest that systemic inflammation, traditional predisposing factors for VTE, as well as potential SARS-CoV2–COVID-19 endothelium interaction likely predispose to VTE and ATE in patients with severe COVID-19. Therefore, physicians should be aware of these complications and remain vigilant for signs of VTE and ATE in the context of the current pandemic.

With the number of identified COVID-19 cases increasing worldwide, it has become clear that infected patients may present in a number of ways. Early observational studies suggested that virtually all patients had parenchymal abnormalities on chest CT.<sup>113</sup> Interestingly, however, pulmonary vascular thickening were also frequently observed in COVID-19 compared with

non-COVID-19 pneumonia, implying a potential tropism of the virus for the pulmonary vasculature.<sup>114</sup> This is not surprising since the SARS-CoV-2 interacts with its functional receptor from the host cells, the ACE 2 receptor,<sup>115</sup> also present on the surface of endothelial cells of virtually all organs, but predominantly within the heart, lungs and kidneys.<sup>116</sup> Consistently, diffuse lymphocytic endotheliitis, endothelial dysfunction and apoptosis resulting from direct viral infection have been reported within the lungs and other organs.<sup>117</sup> Subsequently, observational studies suggested that VTE was common among patients with COVID-19 admitted to the ICU as well as a common autopsy finding following COVID-19-positive deaths despite systematic thrombosis prophylaxis.<sup>118</sup>

The present meta-analysis is consistent with these early descriptions. Interestingly, however, the VTE prevalence varied widely between included series. A major cause of these fluctuations was the study design: patients admitted to the ICU had a twofold increased risk of VTE compared with those admitted on general wards.<sup>14 99</sup> Not surprisingly, asymptomatic screening was also associated with a higher VTE prevalence compared with symptomatic testing only. Other risk factors associated with VTE reported in series included increasing age,<sup>15</sup> lymphopenia,<sup>15 34</sup> male sex,<sup>14 34</sup> increased D-dimer,<sup>15 34 60 99</sup> increased

**Table 2** Metaregression to explore heterogeneity in estimate of venous thromboembolism prevalence

	Studies (n)	Beta (95% CI)*	Intercept†	P value	R <sup>2</sup> (%)
Number of patients‡	56	−0.0082 (−0.0143 to −0.0021)	0.1929	0.008	11
Proportion of patients in ICU	56	0.0017 (0.0008 to 0.0025)	0.0816	<0.0001	28
MINORS score	31	0.0066 (−0.0065 to 0.0197)	0.1212	0.32	0
D-dimers§	30	0.0027 (0.0004 to 0.0051)	0.1183	0.02	14
Proportion of patients receiving anticoagulation	38	0.0016 (−0.0013 to 0.0044)	0.0311	0.29	0
Proportion of men	40	0.0042 (−0.0002 to 0.0087)	−0.0833	0.06	5

R<sup>2</sup> estimates the amount of heterogeneity accounted for by the moderators.

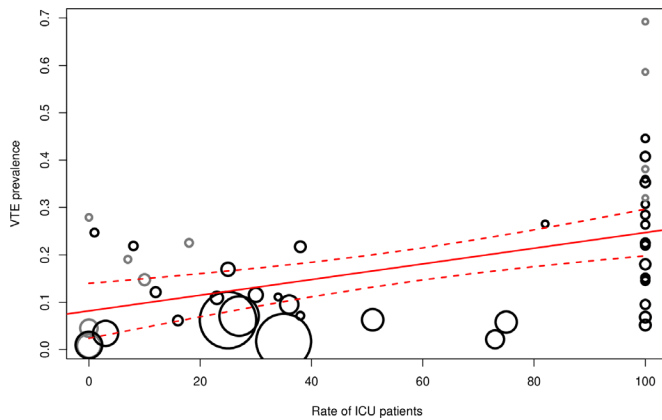
\*Beta signification: prevalence increase or decrease for the augmentation of one unit of the variable tested.

†Intercept signification: rate of venous thromboembolism for a variable with null value.

‡Per increase of 100 patients.

§Per increase of 100 µg/L.

ICU, intensive care unit; MINORS, Methodological Index for Non-randomised Studies.



**Figure 3** Metaregression of the VTE probability according to the rate of patients admitted in ICU. Circles indicate the design of studies included in the metaregression, black for studies testing symptomatic patients and grey for those using systematic screening. The size of the circles correspond to the study size. The red solid curve indicates the prediction of VTE prevalence. The red broken curves indicate the 95% CI of model prediction of VTE prevalence. ICU, intensive care unit; VTE, venous thromboembolism.

activated partial thromboplastin time,<sup>15</sup> invasive mechanical ventilation,<sup>14</sup> as well as high levels of plasma factor VIII activity<sup>60</sup> and factor Willebrand antigen.<sup>60</sup> Interestingly, the exact mechanisms resulting in PE in severe COVID-19 have been questioned. Indeed, disseminated intravascular coagulation, a condition characterised by the generation of microthrombi in different organs, including the pulmonary circulation,<sup>119</sup> has been frequently reported in non-survivors of COVID-19.<sup>120–122</sup> Pulmonary microthrombi were also reported at lung dissection from critically ill patients with COVID-19.<sup>2</sup> This is in line with the immunothrombosis model, which highlights the bidirectional relationship between the immune system and thrombin generation during severe infection<sup>123</sup> and the pathogenesis of acute respiratory distress syndrome.<sup>124</sup> The mechanisms involved in COVID-19-related thrombosis nonetheless remain unclear and may include, in addition to classical pulmonary thromboemboli, intravascular coagulopathy,<sup>1118 125 126</sup> systemic and endothelial inflammation promoting factor Willebrand antigen, fibrinogen and factor VIII activity,<sup>51</sup> immune-mediated damage by anti-phospholipid antibodies<sup>51 127</sup> and hypoxaemia-induced vascular occlusion.<sup>51 128</sup>

**Table 3** Multivariable analysis of 47 studies reporting prevalence of venous thromboembolism

	Beta*	95% CI	Intercept†	P value
Proportion of patients in ICU (%)	0.0020	0.0012 to 0.0028	0.0351	<0.0001
Systematic screening (yes/no)	0.1423	0.0590 to 0.2256	0.0351	0.0008

Number of patients (47 studies,  $p=0.57$ ) and D-dimer level (28 studies,  $p=0.26$ ) were not significantly associated with venous thromboembolism when added to the model.

As an example, the prevalence of venous thromboembolism in a cohort using systematic screening and including 30% of patients in the ICU is estimated at  $0.0351 + 0.1423 + 0.0020 \times 30 = 0.2374$  (23.7%).

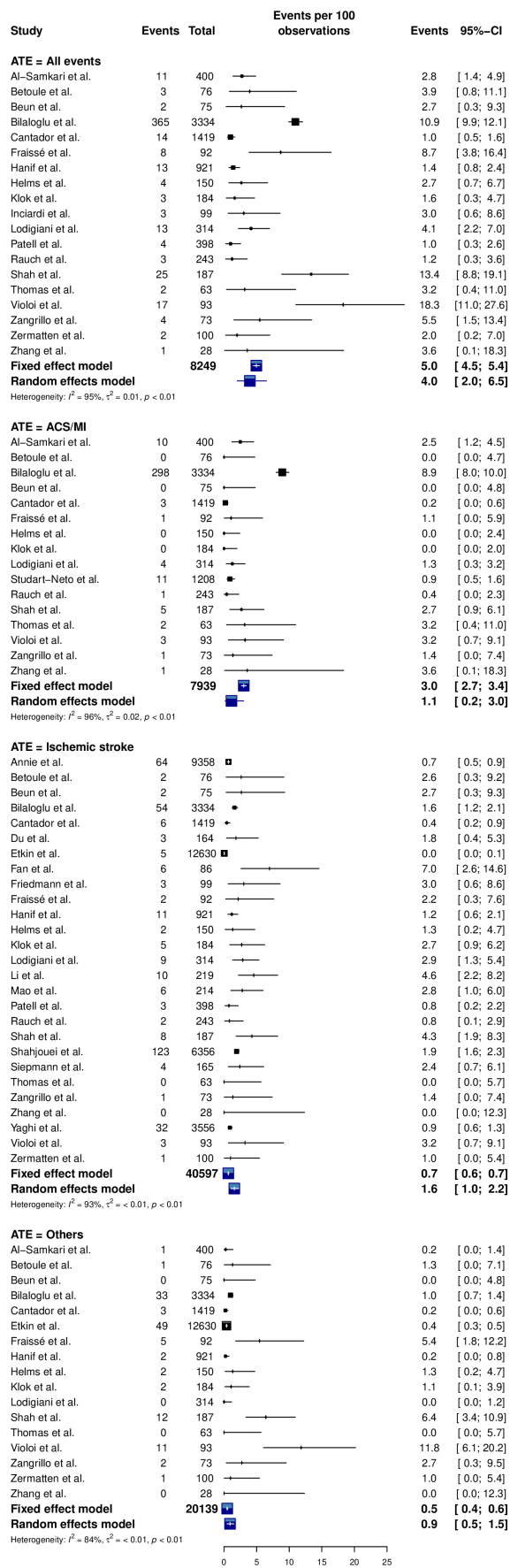
\*Beta signification: prevalence increase or decrease for the augmentation of one unit of the variable tested.

†Intercept signification: rate of venous thromboembolism for all variables with null value.

ICU, intensive care unit.

Importantly, a recent study suggested that the pre-emptive anticoagulation with heparin was associated with decreased mortality among patients with significant sepsis-induced coagulopathy or markedly elevated D-dimer levels.<sup>129</sup> Whether these beneficial effects were related to non-anticoagulant properties of heparin, including its anti-inflammatory,<sup>130</sup> antiviral<sup>131</sup> and protective effects on the pulmonary endothelium, remained unknown.<sup>132</sup> As recognised by the authors, however, this retrospective study was subjected to bias, and its results were not replicated in subsequent studies, suggesting that conventional thromboembolic prophylaxis or therapeutic anticoagulant had limited effects on VTE risk in patients with severe COVID-19.<sup>5 99</sup> Moreover, while the prevalence of VTE and ATE appears substantial, a previous series of 113 patients with severe sepsis and septic shock hospitalised in the ICU reported a VTE prevalence of 37.2%.<sup>133</sup> Consistently, the prevalence of VTE for patients receiving thromboprophylaxis while hospitalised on general wards for other medical illnesses,<sup>134 135</sup> as well as the ATE risk of patients with community-acquired pneumonia,<sup>136 137</sup> was somewhat similar to that observed in patients with COVID-19 in the present meta-analysis. In the context of the increased risk of bleeding<sup>138</sup> and previous negative trials of endogenous anticoagulants in sepsis,<sup>139</sup> these indirect comparisons question the recent recommendations for an early therapeutic anticoagulation for patients with sepsis-related coagulopathy in the context of severe COVID-19.<sup>8 9</sup> As a result, the efficacy, dosage and characteristics of patients most suitable for high-prophylactic doses or systemic anticoagulation remain to be demonstrated in prospective controlled studies before they become standard of care in patients who may also be at increased bleeding risk.<sup>4 17 48 50 85 99</sup>

The present study has some limitations. First, we only partially explained the high level of heterogeneity across studies for VTE. In other words, the estimates of VTE rate cannot be used to compute the individualised risk of a given patient admitted in the general ward or the ICU. Second, the prevalence may have been overestimated due to design, sampling, measurement, confounder and information biases. For example, follow-up duration was limited to the first few weeks following ICU admission, which is associated with the highest thrombotic risk.<sup>34 53</sup> A high number of CT scans were also likely performed for COVID-19, with PE events being potentially observed as an incidental findings only. The increasing awareness about the association between COVID-19 and VTE-ATE may have also lowered the physicians' threshold for ordering imaging studies, especially in case of suspected PE in patients in the ICU. Although sensitivity analyses excluding the two studies<sup>17 64</sup> reporting potential PE using echocardiography yielded similar estimates for PE prevalence (data not shown), this method may have inflated the number of true PE in the context of ICU. Conversely, patients spuriously diagnosed as having COVID-19 may have been included, leading to potential underestimation of the true prevalence of thrombotic events if their conditions were associated with a lower risk of thrombosis. Third, given the high mortality in patients in the ICU, crude estimates may have biased thrombosis prevalence in patients in the ICU,<sup>140</sup> unless competing risk is modelled as reported in three studies.<sup>18 34 53</sup> Fourth, an assessment of the methodological quality showed deficiencies in most included studies. Accordingly, many of the studies were retrospective, combined with other limitations and could thus have led to overestimation of the true VTE-ATE prevalence. Finally, we could not exclude publication bias, given the results of Egger's regression test and funnel plot, although the asymmetry of funnel plot may be related to the smaller ICU cohorts being at increased risk of VTE.<sup>141</sup>



**Figure 4** Forest plot showing the pooled, weighted frequency of patients with ATE. Others included visceral and limb ischaemia. ACS, acute coronary syndrome; ATE, arterial thromboembolic event; MI, myocardial infarction.

In conclusion, patients admitted in the ICU for COVID-19 appear to have a high risk of VTE. Physicians should therefore have a high index of suspicion, especially in patients with some dissociation between relatively well-preserved lung mechanics and significant hypoxaemia. However, the optimal management for VTE prevention and treatment remains to be defined. Moreover, further studies are also needed to determine the specific effects of COVID-19 on the risk of ATE and VTE, especially in less severe forms of the disease.

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**Correction notice** This article has been corrected since it was published Online First. Affiliations for LB have been updated.

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#### REFERENCES

- McGonagle D, O'Donnell JS, Sharif K, *et al*. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020;2:e437–45.
- Lippi G, Favaloro EJ. D-Dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost* 2020;120:876–8.
- Danzi GB, Loffi M, Galeazzi G, *et al*. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J* 2020;41:41.
- Cattaneo M, Bertinato EM, Bircocchi S, *et al*. Pulmonary embolism or pulmonary thrombosis in COVID-19? is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb Haemost* 2020;120:1230–2.
- Litjens J-F, Leclerc M, Chochois C, *et al*. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18:1743–6.
- Klok FA, Kruij MJHA, van der Meer NJM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–7.
- Thomas W, Varley J, Johnston A, *et al*. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. *Thromb Res* 2020;191:76–7.
- Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18:1023–6.
- Bikdeli B, Madhavan MV, Jimenez D, *et al*. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:2950–73.
- Cumpston M, Li T, Page MJ, *et al*. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019;10:CD000142.
- Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- Slim K, Nini E, Forestier D, *et al*. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003;73:712–6.
- Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-Analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.
- Grillet F, Behr J, Calame P, *et al*. Acute pulmonary embolism associated with COVID-19 pneumonia detected with pulmonary CT angiography. *Radiology* 2020;296:E186–8.
- Cui S, Chen S, Li X, *et al*. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:1421–4.
- Gagnier JJ, Morgenstern H, Altman DG, *et al*. Consensus-Based recommendations for investigating clinical heterogeneity in systematic reviews. *BMC Med Res Methodol* 2013;13:106.
- Al-Samkari H, Karp Leaf RS, Dzik WH, *et al*. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020;136:489–500.
- Bilaloglu S, Aphinyanaphongs Y, Jones S, *et al*. Thrombosis in hospitalized patients with COVID-19 in a new York City health system. *JAMA* 2020;324:799.
- Artifoni M, Danic G, Gautier G, *et al*. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 2020;50:211–6.
- Aversa M, Benvenuto L, Anderson M, *et al*. COVID-19 in lung transplant recipients: a single center case series from New York City. *Am J Transplant* 2020;20:3072–80.
- Choi JJ, Wehmeyer GT, Li HA, *et al*. D-Dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. *Thromb Res* 2020;196:318–21.
- Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, *et al*. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res* 2020;192:23–6.
- Dubois-Silva Álvaro, Barbagelata-López C, Mena Álvaro, *et al*. Pulmonary embolism and screening for concomitant proximal deep vein thrombosis in noncritically ill hospitalized patients with coronavirus disease 2019. *Intern Emerg Med* 2020;15:865–70.
- Dumantepe M, Aydin S, Yildiz E. Withdrawn: subsegmental thrombus in COVID-19 pneumonia: Immuno-Thrombosis or pulmonary embolism? data analysis of hospitalized patients with coronavirus disease. *Heart Lung and Circulation* 2020;395:30435–2.
- Galeano-Valle F, Oblitas CM, Ferreira-Mazón MM, *et al*. Antiphospholipid antibodies are not elevated in patients with severe COVID-19 pneumonia and venous thromboembolism. *Thromb Res* 2020;192:113–5.
- Giorgi-Pierfranceschi M, Paoletti O, Pan A. Prevalence of asymptomatic deep vein thrombosis in patients hospitalized with SARS-CoV-2 pneumonia: a cross-sectional study. *Intern Emerg Med* 2020.
- Hanif A, Khan S, Mantri N, *et al*. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a new York City Hospital experience. *Ann Hematol* 2020;99:2323–8.



- 28 Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:e393–400.
- 29 Kartsios C, Lokare A, Osman H, et al. Diagnosis, management, and outcomes of venous thromboembolism in COVID-19 positive patients: a role for direct anticoagulants? *J Thromb Thrombolysis* 2020;1–6.
- 30 Le Jeune S, Suhli J, Benainou R, et al. High prevalence of early asymptomatic venous thromboembolism in anticoagulated COVID-19 patients hospitalized in general wards. *J Thromb Thrombolysis* 2020. doi:10.1007/s11239-020-02246-w. [Epub ahead of print: 18 Aug 2020].
- 31 Marone EM, Bonalumi G, Curci R, et al. Characteristics of venous thromboembolism in COVID-19 patients: a multicenter experience from northern Italy. *Ann Vasc Surg* 2020;68:83–7.
- 32 Mattioli M, Benfaremo D, Mancini M, et al. Safety of intermediate dose of low molecular weight heparin in COVID-19 patients. *J Thromb Thrombolysis* 2020. doi:10.1007/s11239-020-02243-z. [Epub ahead of print: 13 Aug 2020].
- 33 Mei F, Fan J, Yuan J, et al. Comparison of venous thromboembolism risks between COVID-19 pneumonia and community-acquired pneumonia patients. *Arterioscler Thromb Vasc Biol* 2020;40:2332–7.
- 34 Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;18:1995–2002.
- 35 Naymagon L, Zubizarreta N, Feld J, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. *Thromb Res* 2020;196:99–105.
- 36 Patell R, Bogue T, Bindal P, et al. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. *J Thromb Haemost* 2020;18:2349–57.
- 37 Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. *J Thromb Haemost* 2020;18:2629–35.
- 38 Pizzolo F, Rigoni AM, De Marchi S, et al. Deep vein thrombosis in SARS-CoV-2 pneumonia-affected patients within standard care units: exploring a submerged portion of the iceberg. *Thromb Res* 2020;194:216–9.
- 39 Rauch A, Labreuche J, Lassalle F, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. *J Thromb Haemost* 2020;18:2942–53.
- 40 Rali P, O'Corragain O, Oresanya L, et al. Incidence of venous thromboembolism in coronavirus disease 2019: an experience from a single large academic center. *J Vasc Surg Venous Lymphat Disord* 2020. doi:10.1016/j.jvs.2020.09.006. [Epub ahead of print: 05 Oct 2020].
- 41 Rieder M, Goller I, Jeserich M, et al. Rate of venous thromboembolism in a prospective all-comers cohort with COVID-19. *J Thromb Thrombolysis* 2020;50:558–66.
- 42 Siepmann T, Sedghi A, Simon E, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. *Eur J Neurol* 2021;28:238–47.
- 43 Stoneham SM, Milne KM, Nuttall E, et al. Thrombotic risk in COVID-19: a case series and case-control study. *Clin Med* 2020;20:e76–81.
- 44 Trimaille A, Curtaud A, Marchandot B, et al. Venous thromboembolism in non-critically ill patients with COVID-19 infection. *Thromb Res* 2020;193:166–9.
- 45 Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020;31:894–901.
- 46 Aleva FE, van Mourik L, Broeders MEAC, et al. COVID-19 in critically ill patients in North Brabant, the Netherlands: patient characteristics and outcomes. *J Crit Care* 2020;60:111–5.
- 47 Beun R, Kusadasi N, Sikma M, et al. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *Int J Lab Hematol* 2020;42:19–20.
- 48 Desborough MJR, Doyle AJ, Griffiths A, et al. Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. *Thromb Res* 2020;193:1–4.
- 49 Grandmaison G, Andrey A, Périard D, et al. Systematic screening for venous thromboembolic events in COVID-19 pneumonia. *TH Open* 2020;04:e113–5.
- 50 Fraissé M, Logre E, Pajot O, et al. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. *Crit Care* 2020;24:275.
- 51 Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46:1089–98.
- 52 Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. *Br J Haematol* 2020;190.
- 53 Klok FA, Kruij MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res* 2020;191:148–50.
- 54 Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in northern Italy. *Eur Heart J* 2020;41:1821–9.
- 55 Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020;191:9–14.
- 56 Longchamp A, Longchamp J, Manzocchi-Besson S, et al. Venous thromboembolism in critically ill patients with COVID-19: results of a screening study for deep vein thrombosis. *Res Pract Thromb Haemost* 2020;4:842–7.
- 57 Longhitano Y, Racca F, Zanza C, et al. Venous thromboembolism in critically ill patients affected by ARDS related to COVID-19 in Northern-West Italy. *Eur Rev Med Pharmacol Sci* 2020;24:9154–60.
- 58 Maatman TK, Jalali F, Feizpour C, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. *Crit Care Med* 2020;48:e783–90.
- 59 Pavoni V, Giansello L, Pazzi M, et al. Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: a call to action. *Thromb Res* 2020;196:313–7.
- 60 Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation* 2020;142:184–6.
- 61 Shah A, Donovan K, McHugh A, et al. Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. *Crit Care* 2020;24:561.
- 62 Stefely JA, Christensen BB, Gogakos T, et al. Marked factor V activity elevation in severe COVID-19 is associated with venous thromboembolism. *Am J Hematol* 2020;95:1522–30.
- 63 Taccone FS, Gevenois PA, Peluso L, et al. Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically ill coronavirus disease 2019 patients. *Crit Care Med* 2020;48:e1087–90.
- 64 Tavazzi G, Civaridi L, Caneva L, et al. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Med* 2020;46:1121–3.
- 65 Violi F, Ceccarelli G, Cangemi R, et al. Hypoalbuminemia, coagulopathy, and vascular disease in COVID-19. *Circ Res* 2020;127:400–1.
- 66 Zangrillo A, Beretta L, Scandroglio AM. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc* 2020. [Epub ahead of print: 23 Apr 2020].
- 67 Zermatten MG, Pantet O, Gomez F, et al. Utility of D-dimers and intermediate-dose prophylaxis for venous thromboembolism in critically ill patients with COVID-19. *Thromb Res* 2020;196:222–6.
- 68 Piagnerelli M, Cauchie P, Vancutsem M, et al. Thromboprophylaxis in critically ill coronavirus disease 2019 patients. *Crit Care Explor* 2020;2:e0177.
- 69 Alharthy A, Faqih F, Memish ZA, et al. Lung injury in COVID-19: An emerging hypothesis. *ACS Chem Neurosci* 2020;11:2156–8.
- 70 Beyls C, Huetter P, Abou-Arab O, et al. Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome and risk of thrombosis. *Br J Anaesth* 2020;125:e260–2.
- 71 Mueller-Peltzer K, Krauss T, Benndorf M, et al. Pulmonary artery thrombi are co-located with opacifications in SARS-CoV2 induced ARDS. *Respir Med* 2020;172:106135.
- 72 Soumagne T, Lascarrou J-B, Hraiech S, et al. Factors associated with pulmonary embolism among coronavirus disease 2019 acute respiratory distress syndrome: a multicenter study among 375 patients. *Crit Care Explor* 2020;2:e0166.
- 73 Whyte MB, Kelly PA, Gonzalez E, et al. Pulmonary embolism in hospitalised patients with COVID-19. *Thromb Res* 2020;195:95–9.
- 74 Alonso-Fernández A, Toledo-Pons N, Cosío BG, et al. Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: a prospective study. *PLoS One* 2020;15:e0238216.
- 75 Benito N, Filella D, Mateo J, et al. Pulmonary thrombosis or embolism in a large cohort of hospitalized patients with Covid-19. *Front Med* 2020;7:557.
- 76 Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020;56:2001365. doi:10.1183/13993003.01365-2020
- 77 Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020;76:43–9.
- 78 Espallargas I, Rodríguez Sevilla JJ, Rodríguez Chiaradía DA. Ct imaging of pulmonary embolism in patients with COVID-19 pneumonia: a retrospective analysis. *Eur Radiol* 2020;39:51–8.
- 79 Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicenter cohort study. *Eur Heart J* 2020;41:3058–68.
- 80 Freund Y, Drogrey M, Miró Óscar, et al. Association between pulmonary embolism and COVID-19 in emergency department patients undergoing computed tomography pulmonary angiogram: the PEPCOV international retrospective study. *Acad Emerg Med* 2020;27:811–20.
- 81 Gervaise A, Bouzad C, Peroux E, et al. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CtpA by emergency department. *Eur Radiol* 2020;30:6170–7.
- 82 Larsen K, Coolen-Allou N, Masse L, et al. Detection of pulmonary embolism in returning travelers with hypoxic pneumonia due to COVID-19 in reunion island. *Am J Trop Med Hyg* 2020;103:844–6.
- 83 Lendorf ME, Boisen MK, Kristensen PL, et al. Characteristics and early outcomes of patients hospitalised for COVID-19 in North Zealand, Denmark. *Dan Med J* 2020;67:A06200428.

- 84 Mestre-Gómez B, Lorente-Ramos RM, Rogado J, *et al.* Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. *J Thromb Thrombolysis* 2021;51:40–6.
- 85 Moll M, Zon RL, Sylvester KW, *et al.* Vte in ICU patients with COVID-19. *Chest* 2020;158:2130–5.
- 86 Monfardini L, Morassi M, Botti P, *et al.* Pulmonary thromboembolism in hospitalised COVID-19 patients at moderate to high risk by wells score: a report from Lombardy, Italy. *Br J Radiol* 2020;93:20200407.
- 87 Mouhat B, Besutti M, Bouiller K, *et al.* Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. *Eur Respir J* 2020;56:2001811.
- 88 Zhang P, Qu Y, Tu J. Applicability of bedside ultrasonography for the diagnosis of deep venous thrombosis in patients with COVID-19 and treatment with low molecular weight heparin. *J Clin Ultrasound* 2020. [Epub ahead of print: 05 Aug 2020].
- 89 Nahum J, Morichau-Beauchant T, Daviaud F, *et al.* Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19). *JAMA Netw Open* 2020;3:e2010478.
- 90 Ren B, Yan F, Deng Z, *et al.* Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. *Circulation* 2020;142:181–3.
- 91 Torres-Machorro A, Anguiano-Álvarez VM, Grimaldo-Gómez FA, *et al.* Asymptomatic deep vein thrombosis in critically ill COVID-19 patients despite therapeutic levels of anti-Xa activity. *Thromb Res* 2020;196:268–71.
- 92 Trigonis RA, Holt DB, Yuan R, *et al.* Incidence of venous thromboembolism in critically ill coronavirus disease 2019 patients receiving prophylactic anticoagulation. *Crit Care Med* 2020;48:e805–8.
- 93 Voicu S, Bonnin P, Stéphanian A, *et al.* High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients. *J Am Coll Cardiol* 2020;76:480–2.
- 94 Yu B, Li X, Chen J, *et al.* Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis* 2020;50:548–57.
- 95 Beigel JH, Tomashek KM, Dodd LE, *et al.* Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020;383:1813–26.
- 96 Bozzani A, Tavazzi G, Arici V, *et al.* Acute deep vein thrombosis in COVID 19 hospitalized patients. risk factors and clinical outcomes. *Phlebology* 2020;268355520958598.
- 97 Jimenez-Guiu X, Huici-Sánchez M, Romera-Villegas A, *et al.* Deep vein thrombosis in non-critically ill patients with coronavirus disease 2019 pneumonia: deep vein thrombosis in non-intensive care unit patients. *J Vasc Surg Venous Lymphat Disord* 2020;30466–2.
- 98 Xing C, Li Q, Du H, *et al.* Lung ultrasound findings in patients with COVID-19 pneumonia. *Crit Care* 2020;24.
- 99 Léonard-Lorant I, Delabranche X, Séverac F, *et al.* Acute pulmonary embolism in patients with COVID-19 at CT angiography and relationship to D-dimer levels. *Radiology* 2020;296:E189–91.
- 100 Santoliquido A, Porfida A, Nesci A, *et al.* Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *J Thromb Haemost* 2020;18:2358–63.
- 101 Betoule A, Martinet C, Gasperini G, *et al.* Diagnosis of venous and arterial thromboembolic events in COVID-19 virus-infected patients. *J Thromb Thrombolysis* 2020;50:302–4.
- 102 Cantador E, Núñez A, Sobrino P, *et al.* Incidence and consequences of systemic arterial thrombotic events in COVID-19 patients. *J Thromb Thrombolysis* 2020;50:543–7.
- 103 Studart-Neto A, Guedes BF, Tuma RdeLE, *et al.* Neurological consultations and diagnoses in a large, dedicated COVID-19 university hospital. *Arq Neuropsiquiatr* 2020;78:494–500.
- 104 Annie F, Bates MC, Nanjundappa A, *et al.* Prevalence and outcomes of acute ischemic stroke among patients  $\leq 50$  years of age with laboratory confirmed COVID-19 infection. *Am J Cardiol* 2020;130:169–70.
- 105 Du H, Pan X, Liu N, *et al.* The effect of vascular risk factor burden on the severity of COVID-19 illness, a retrospective cohort study. *Respir Res* 2020;21:241.
- 106 Etkin Y, Conway AM, Silpe J, *et al.* Acute arterial thromboembolism in patients with COVID-19 in the new York City area. *Ann Vasc Surg* 2021;70:290–4.
- 107 Fan S, Xiao M, Han F, *et al.* Neurological manifestations in critically ill patients with COVID-19: a retrospective study. *Front Neurol* 2020;11:806.
- 108 Fridman S, Bres Bullrich M, Jimenez-Ruiz A, *et al.* Stroke risk, phenotypes, and death in COVID-19: systematic review and newly reported cases. *Neurology* 2020;95:e3373–85.
- 109 Li Y, Li M, Wang M, *et al.* Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020;5:279–84.
- 110 Mao L, Jin H, Wang M, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683.
- 111 Shahjouei S, Naderi S, Li J, *et al.* Risk of stroke in hospitalized SARS-CoV-2 infected patients: a multinational study. *Ebiomedicine* 2020;59:102939.
- 112 Yaghi S, Ishida K, Torres J, *et al.* SARS-CoV-2 and stroke in a new York healthcare system. *Stroke* 2020;51:2002–11.
- 113 Ai T, Yang Z, Hou H, *et al.* Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology* 2020;296:E32–40.
- 114 Bai HX, Hsieh B, Xiong Z, *et al.* Performance of radiologists in differentiating COVID-19 from Non-COVID-19 viral pneumonia at chest CT. *Radiology* 2020;296:E46–54.
- 115 Wrapp D, Wang N, Corbett KS, *et al.* Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260–3.
- 116 Hamming I, Timens W, Bulthuis MLC, *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
- 117 Varga Z, Flammer AJ, Steiger P, *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–8.
- 118 Wichmann D, Sperhake J-P, Lütgehetmann M, *et al.* Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020;173:268–77.
- 119 Luo W, Yu H, Gou J. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19), 2020. Available: <https://www.preprints.org/manuscript/202002.0407/v1> [Accessed 19 May 2020].
- 120 Tang N, Li D, Wang X, *et al.* Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7.
- 121 Paranjpe I, Fuster V, Lala A, *et al.* Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020;76:122–4.
- 122 Tremblay D, van Gerwen M, Alsen M, *et al.* Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. *Blood* 2020;136:144–7.
- 123 Gaertner F, Massberg S. Blood coagulation in immunothrombosis-At the frontline of intravascular immunity. *Semin Immunol* 2016;28:561–9.
- 124 Ozolina A, Sarkele M, Sabelnikov O, *et al.* Activation of coagulation and fibrinolysis in acute respiratory distress syndrome: a prospective pilot study. *Front Med* 2016;3:64.
- 125 Levi M, Thachil J, Iba T, *et al.* Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020;7:e438–40.
- 126 Panigada M, Bottino N, Tagliabue P, *et al.* Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020;18:1738–42.
- 127 Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with COVID-19. *J Thromb Haemost* 2020;18:2064–5.
- 128 Grimmer B, Kuebler WM. The endothelium in hypoxic pulmonary vasoconstriction. *J Appl Physiol* 2017;123:1635–46.
- 129 Tang N, Bai H, Chen X, *et al.* Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020;18:1094–9.
- 130 Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res* 2008;122:743–52.
- 131 Shukla D, Spear PG. Herpesviruses and heparan sulfate: an intimate relationship in aid of viral entry. *J Clin Invest* 2001;108:503–10.
- 132 Iba T, Hashiguchi N, Nagaoka I, *et al.* Heparins attenuated histone-mediated cytotoxicity in vitro and improved the survival in a rat model of histone-induced organ dysfunction. *Intensive Care Med* 2015;3:36.
- 133 Kaplan D, Casper TC, Elliott CG, *et al.* Vte incidence and risk factors in patients with severe sepsis and septic shock. *Chest* 2015;148:1224–30.
- 134 Cohen AT, Harrington RA, Goldhaber SZ, *et al.* Extended thromboprophylaxis with Betrixaban in acutely ill medical patients. *N Engl J Med* 2016;375:534–44.
- 135 Kakkar AK, Cimminiello C, Goldhaber SZ, *et al.* Low-Molecular-Weight heparin and mortality in acutely ill medical patients. *N Engl J Med* 2011;365:2463–72.
- 136 Tralh e Ant nio, P voa P, Tralh o A, *et al.* Cardiovascular events after community-acquired pneumonia: a global perspective with systematic review and meta-analysis of observational studies. *JCM* 2020;9:414.
- 137 Ramirez J, Aliberti S, Mirsaeidi M, *et al.* Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis* 2008;47:182–7.
- 138 Wang T, Chen R, Liu C, *et al.* Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol* 2020;7:e362–3.
- 139 Warren BL, Eid A, Singer P, *et al.* Caring for the critically ill patient. high-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869–78.
- 140 Mainbourg S, Cucherat M, Lega J-C. Analysis of incidence of thrombotic complications in the presence of competing risks. *Thromb Res* 2020;191:152.
- 141 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.