Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19

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ABSTRACT

Background: The incidence of venous thromboembolic events (VTE) in patients with COVID-19 is generally high but varies markedly. However, the relationship between anticoagulation and mortality in patients with COVID-19 is still unclear.
Methods: We performed a systematic review and meta-analysis to determine the incidence of VTE and evaluate the role of anticoagulation in patients with COVID-19. Random effects models were used to determine overall pooled estimates and 95% confidence intervals (CIs).
Results: After a database search, 25 observational studies (20 on VTE incidence and 5 on the relationship between anticoagulation and mortality) were included. The pooled incidence rates of VTE, pulmonary embolism (PE), and deep vein thrombosis (DVT) in hospitalised COVID-19 patients were 21% (95% CI 15–27%), 15% (95% CI 10–20%), and 27% (95% CI 19–36%), respectively. A meta-analysis of five studies found that anticoagulation was not associated with an increased risk of mortality in hospitalised COVID-19 patients (RR = 0.86, 95% CI, 0.69–1.09, P = 0.218; I^2 = 47.4%).
Conclusions: In conclusion, the incidence of VTE among hospitalised COVID-19 patients was high. Clinical trials are urgently needed to evaluate the roles of prophylactic and therapeutic anticoagulation in COVID-19.

Introduction

Since the outbreak of COVID-19 in December 2019, more than 6 million confirmed cases and 392,000 deaths have been reported worldwide as of June 1, 2020(1). Aside from the lungs, this disease may also cause severe injury to the heart (Li et al., 2020), kidneys (Ronco et al., 2020), and liver (Mao et al., 2020) that can lead to death.

Emerging data suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also targets the haematological system (Iba et al., 2020). Venous thromboembolic events (VTE) were reported in a case series of COVID-19 patients (Koumoutsea et al., 2020; Zhou et al., 2020; Giacomelli et al., 2020). In a very recent study (Wichmann et al., 2020), autopsies performed on 12 consecutive COVID-19-positive patients revealed that pulmonary embolism (PE) was the direct cause of death in 4 patients. These observations have led to concerns that COVID-19 is associated with a risk of VTE. Increasingly, studies (Al-Samkari et al., 2020; Artifoni et al., 2020; Bompard et al., 2020; Cui et al., 2020; Demelo-Rodriguez et al., 2020; Desborough et al., 2020; Helms et al., 2020; Hippensteel et al., 2020; Klok et al., 2020; Leonard-Lorant et al., 2020; Llitjos et al., 2020; Lodigiani et al., 2020; Middeldorp et al., 2020; Nahum et al., 2020; Poissy et al., 2020; Stoneham et al., 2020; Thomas et al., 2020; Voicu et al., 2020; Zhang et al., 2020) have evaluated the incidence of VTE in COVID-19 patients, which tended to be higher among those in the intensive care unit (ICU). However, the results have been very inconsistent. COVID-19 has been observed to be associated with elevated D-dimer levels and coagulopathy in patients, which increases the risk of death. This suggests that COVID-19 patients without medical contraindications may benefit from anticoagulant treatment. Several

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observational studies (Ayerbe et al., 2020; Paranjpe et al., 2020; Russo et al., 2020; Tang et al., 2020; Tremblay et al., 2020) have investigated the association of anticoagulation with risk of death in COVID-19 patients, with varying results. Therefore, we reviewed the literature and performed a meta-analysis pertaining to this association. This report extends current knowledge by assessing (WHO, 2020) the pooled incidence of VTE [PE or deep vein thrombosis (DVT)] in hospitalised patients with COVID-19 and (Li et al., 2020) determining whether anticoagulant treatment affected mortality.

Methods

To ensure that the work was of high quality, we followed the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) guidelines (Table S1). All steps were performed independently by two investigators with different specialties. Any disagreements were resolved by discussion between the two reviewers, or by a third reviewer.

Search strategy

The PubMed, EMBASE, and Cochrane Library databases were searched to identify all relevant articles published between Jan 1, 2020 and June 4, 2020. The World Health Organization (WHO, 2020) database and medRxiv.org were also searched for potentially relevant publications, including accepted articles yet to be published. The following keywords, and combinations thereof, were searched for: ("Corona Virus Disease-2019″ OR "2019 novel coronavirus" OR "SARS-CoV-2″ OR "COVID-19″ OR "2019-nCoV") AND ("VTE" OR "PE" OR "DVT" OR "thromboembolism" OR "venous thrombosis" OR "pulmonary embolism" OR "deep venous thrombosis" OR "thrombotic" OR "anticoagulants" OR "factor Xa inhibitors" OR "heparinoids" OR "dabigatran" OR "rivaroxaban" OR "edoxaban" OR "apixaban" OR "heparin"). Reference lists of relevant articles were searched manually.

Study selection

We included observational studies that reported the incidence of VTE in hospitalised patients with confirmed COVID-19. Studies not reporting clinical characteristics or clinical experience were excluded, as were case reports.

For studies that evaluated the effects of anticoagulation on mortality in patients with COVID-19, the following inclusion criteria were applied: (WHO, 2020) case–control or cohort study; (Li et al., 2020) no subjects in the reference group receiving anticoagulants; Ronco et al. (2020) odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) of subsequent mortality reported; (Mao et al., 2020) inclusion of adequate data to allow risk estimation; and (Iba et al., 2020) written in English.

Data extraction and quality assessment

For studies that evaluated the rate of VTE in patients with COVID-19, the following information was extracted using a standardised data collection method: author, study origin, design, period, site, baseline characteristics, and number of COVID-19 cases and VTE. Methodological quality was assessed using the instrument of Udina et al., which comprises 10 questions examining research quality. Studies with scores $\geq$15 were considered high quality.

For studies that investigated the impact of anticoagulation on mortality, the following information was extracted using a standardised data collection method: author, study origin, design, period and site, baseline characteristics, number of cases receiving and not receiving anticoagulants, measurement of anticoagulation,

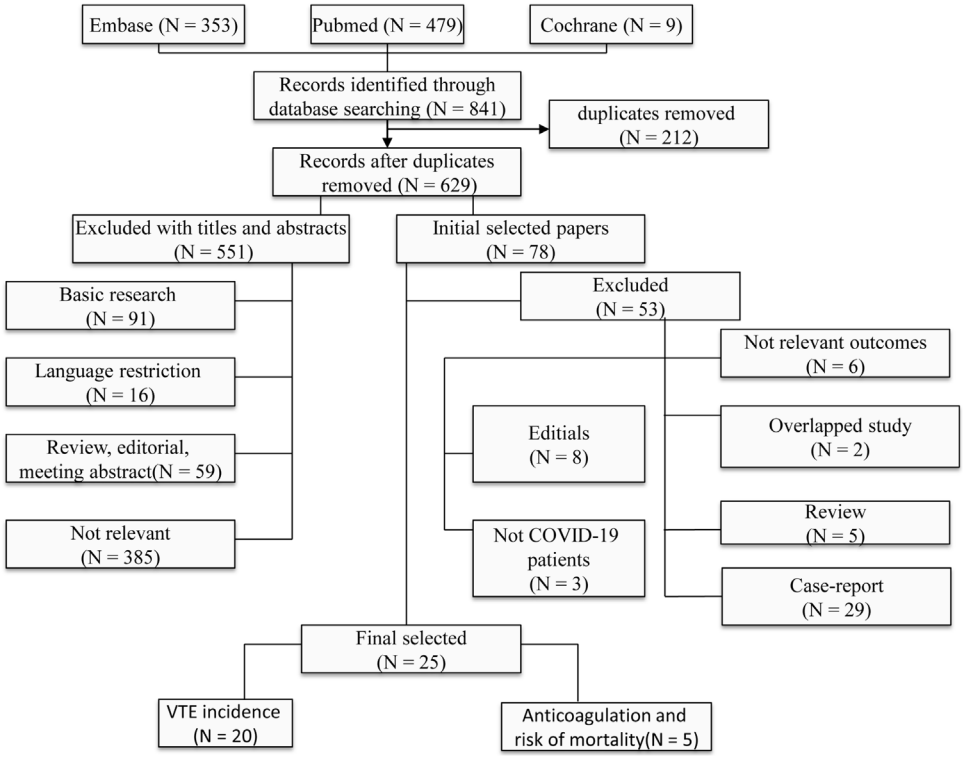

Figure 1. Flow chart of the studies considered and finally selected for review.

and statistical adjustments. The methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) (Higgins, 2014), which has eight criteria and yields scores ranging from 0 (high risk of bias) to 9 (low risk of bias). Studies with scores ≥7 were regarded as high quality.

Statistical analysis

The meta-analysis of the rate of VTE was performed using a random-effects model with the Freeman–Tukey double arcsine transformation applied. The data on mortality risk were pooled using a random effects model with the generic inverse variance method, as described by DerSimonian and Laird (Greenland, 1987). We used the I^2 statistic to assess statistical heterogeneity; an I^2 value >50% was considered to indicate significant heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). Owing to the anticipated heterogeneity of the included studies, we used a random-effects model to estimate effect sizes, which would provide more conservative estimates of the 95% CIs. The statistical analyses were performed using Stata software (ver. 12.0; Stata Corp., College Station, TX, USA).

Results

Search results

The electronic database and manual searches of the reference lists of relevant articles yielded 841 unique articles, and 212 duplicates. In total, 551 articles were excluded after reading the title and abstract. The full text of the remaining 78 articles was assessed in terms of suitability for the meta-analysis. Ultimately, our meta-analysis included 25 studies: 20 on DVT incidence and 5 on anticoagulation in COVID-19 patients. Figure 1 summarises the number of articles by reason for exclusion at each stage of the eligibility assessment.

Characteristics of studies reporting the rate of VTE in COVID-19 patients

Table 1 summarizes the characteristics of the included studies reporting the rate of VTE. Fifteen studies were performed in Europe, two in USA and three in Chinese. The number of COVID-19 patients ranged from 26 to 400. Ten, four and six studies assessed the rate of VTE in patients only in the ICU, in both the ICU and general wards, and only in general wards, respectively. The mean age of the subjects ranged from 57 to 68 years and the proportion

Table 1
Characteristics of the Included Studies.

Author	Country (city)	Study design	Study period	Study site	Age (year)	Male	Outcomes	Number of COVID-19 cases	Quality
Al-Samkari et al (2020)	USA	Retrospective multi-center	Mar 1 to Apr 5 2020	ICU and GW	62.5	57%	VTE	400	17
Artifoni et al (2020)	France (Nantes)	Retrospective multi-center	Mar 25 to Apr 10 2020	GW	64 (46-75)	60%	PE, DVT	71	14
Bompard et al (2020)	France (Paris)	Retrospective multi-center	Mar 1 to Apr 116 2020	ICU and GW	64 (54-76)	70%	PE	135	16
Cui et al (2020)	China (Wuhan)	Retrospective single-center	Jau 30 to Mar 22, 2020	ICU	60 (14.1)	46%	VTE	81	17
Demelo-Rodríguez et al (2020)	Spain (Madrid)	Prospective single-center	First half of April 2020	GW	68.1 (14.5)	65%	DVT	156	16
Desborough et al (2020)	UK (London)	Retrospective single-center	Mar 3 to 31 2020	ICU	59 (49-66)	73%	VTE	66	14
Helms et al (2020)	France (Paris)	Prospective multi-center	Mar 3 to 31 2020	ICU	63 (53-71)	81.00%	PE, DVT	150	17
Hippensteel et al (2020)	USA (Aurora)	Retrospective single-center	Mar 18 to Apr 14 2020	GW	56	58.00%	PE, VTE, DVT	61	14
Klok et al (2020)	Netherlands (Paris)	Retrospective multi-center	Mar 7 to Apr 5 2020	ICU	64 (12)	76%	PE, DVT	184	18
Leonard-Lorant et al (2020)	France (Paris)	Retrospective multi-center	March 1 to 31 2020	ICU and GW	64 (22)	66%	PE	106	14
Llitjos et al (2020)	France (Paris)	Retrospective multi-center	Mar 19 to Apr 11 2020	ICU	68 (51-74)	77%	PE, VTE	26	13
Lodigiani et al (2020).	Italy (Milan)	Retrospective single-center	Feb 13 to Apr 10 2020	ICU	66 (55-85)	68%	PE, VTE, DVT	388	16
Middeldorp et al (2020)	Netherlands (Amsterdam)	Retrospective single-center	Mar 2 to Apr 12, 2020	ICU and GW	61 (14)	66%	PE, VTE, DVT	198	16
Nahum et al (2020)	Germany (Nord)	Retrospective single-center	Mar to Apr 2020	ICU	62 (8.6%)	78%	DVT	34	13
Poissy et al (2020)	France (Lille)	Retrospective single-center	Feb 27 to Mar 31, 2020	ICU	57 (29-80)	59%	PE, DVT	107	15
Ren et al (2020)	China (Wuhan)	Retrospective single-center	Feb 27 to Mar 31, 2020	ICU	57 (62-80)	54%	DVT	48	10
Stoneham et al (2020)	UK (Brighton)	Retrospective multi-center	Mar 20 to Apr 16 2020	ICU and GW	NA	NA	PE, VTE, DVT	274	16
Thomas et al (2020)	UK (Cambridge)	Retrospective single-center	to Apr 14, 2020	ICU	20-89	NA	PE, VTE	63	14
Voicu et al (2020)	France (Paris)	Prospective single-center	Mar 13 to Apr 3 2020	ICU and GW	NA	NA	DVT	56	14
Zhang et al (2020)	China (Wuhan)	Retrospective single-center	Jan 29 to Feb 29, 2020	GW	63 (14)	52%	DVT	143	16

DVT, deep vein thrombosis; GW, general ward; ICU, intensive care unit; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolic event.

of males ranged from 52% to 81%. Table S2 presents the quality assessment results.

VTE incidence

Eleven studies (Al-Samkari et al., 2020; Artifoni et al., 2020; Cui et al., 2020; Desborough et al., 2020; Helms et al., 2020; Hippensteel et al., 2020; Llitjos et al., 2020; Lodigiani et al., 2020; Middeldorp et al., 2020; Stoneham et al., 2020; Thomas et al., 2020) reported the overall incidence of VTE (ICU and general wards), which ranged from 4% to 42%. VTE occurred in 255 of 1808 hospitalised patients. The meta-analysis revealed a pooled incidence rate of VTE of 21% (95% CI 15–27%, I^2 = 94.8%; Figure 2A) among all hospitalised patients. Eight (Al-Samkari et al.,

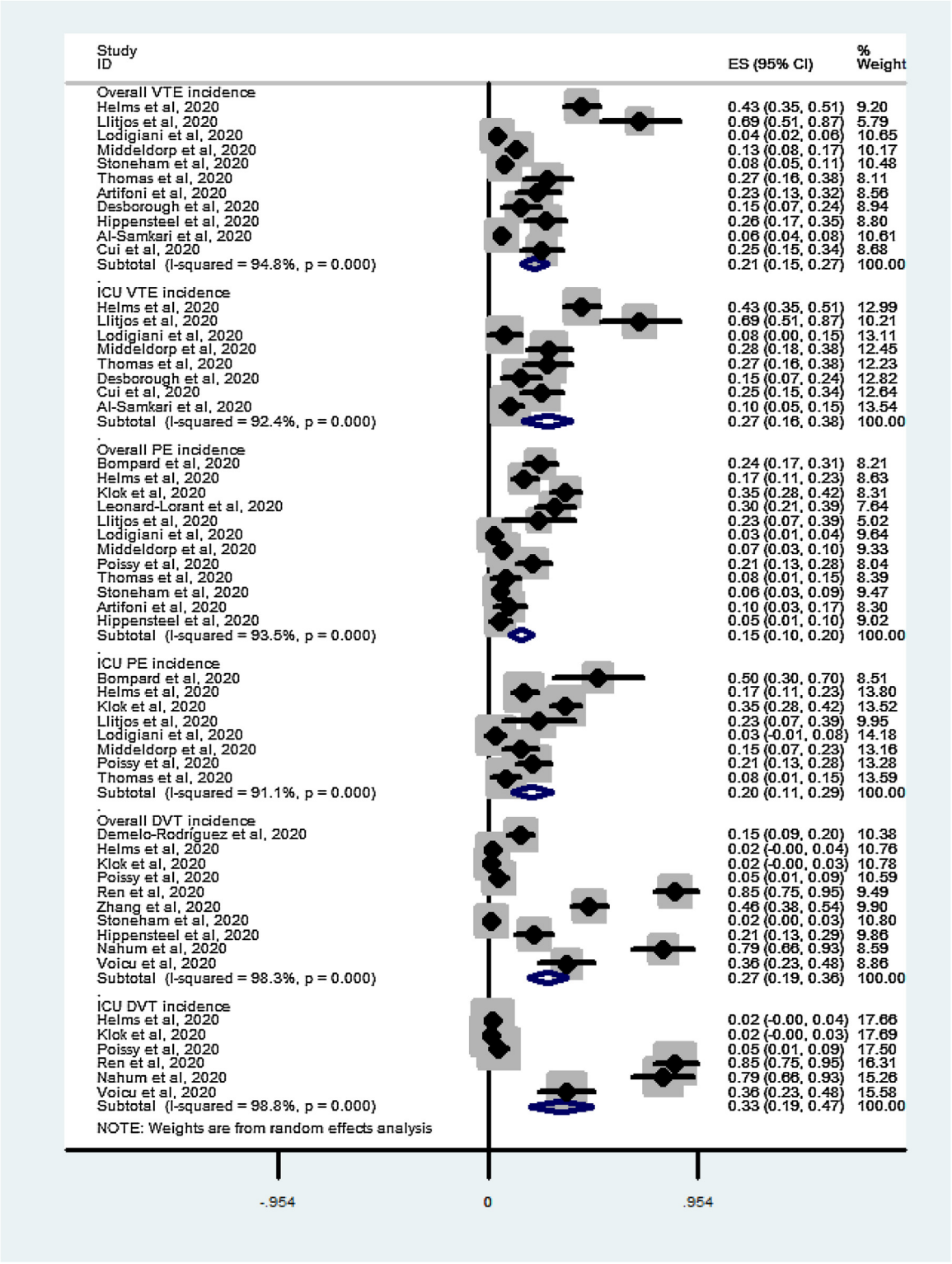

Figure 2. Summary of pooled VTE incidence in COVID-19 patients. (A) VTE in all hospitalised patients; (B) VTE in ICU patients; (C) PE in all hospitalised patients; (D) PE in ICU patients; (E) DVT in all hospitalised patients; (F) DVT in ICU patients.

2020; Cui et al., 2020; Desborough et al., 2020; Helms et al., 2020; Llitjos et al., 2020; Lodigiani et al., 2020; Middeldorp et al., 2020; Thomas et al., 2020) studies reported the incidence of VTE in the ICU setting. VTE occurred in 169 of 656 ICU patients. A meta-analysis of the proportions revealed a pooled incidence of VTE of 27% (95% C.I. 16–38%, I^2 = 92.4%; Figure 2B) among ICU patients.

Twelve studies (Artifoni et al., 2020; Bompard et al., 2020; Helms et al., 2020; Hippensteel et al., 2020; Klok et al., 2020; Leonard-Lorant et al., 2020; Llitjos et al., 2020; Middeldorp et al., 2020; Poissy et al., 2020; Stoneham et al., 2020; Thomas et al., 2020) reported the overall incidence of PE, which varied from 2% to 35%. PE occurred in 238 out of 1793 hospitalised patients. The meta-analysis revealed a pooled incidence rate of PE of 15% (95% CI 10%–20%, I^2 = 93.5%; Figure 2C) among all hospitalised patients. Eight studies (Bompard et al., 2020; Helms et al., 2020; Klok et al., 2020; Llitjos et al., 2020; Lodigiani et al., 2020; Middeldorp et al., 2020; Poissy et al., 2020; Thomas et al., 2020) reported the incidence of PE in the ICU setting. PE occurred in 148 of 690 ICU patients. A meta-analysis of the proportions revealed a pooled incidence of PE of 20% (95% CI 9–31%, I^2 = 49.6%; Figure 2D) among ICU patients.

Nine studies (Demelo-Rodriguez et al., 2020; Helms et al., 2020; Hippensteel et al., 2020; Klok et al., 2020; Nahum et al., 2020; Poissy et al., 2020; Ren et al., 2020; Stoneham et al., 2020; Voicu et al., 2020; Zhang et al., 2020) reported the overall incidence of DVT, which varied from 2% to 85%. DVT occurred in 212 out of 1243 hospitalised patients. The meta-analysis revealed a pooled incidence rate of DVT of 27% (95% CI 19%–36%, I^2 = 98.3%; Figure 2E) among all hospitalised patients. Seven studies (Helms et al., 2020; Klok et al., 2020; Nahum et al., 2020; Voicu et al., 2020) reported the incidence of DVT in the ICU setting. DVT occurred in 99 out of 579 ICU patients. Meta-analysis revealed a pooled incidence of DVT of 33% (95% CI 19%–47%, I^2 = 98.8%; Figure 2F) among ICU patients. (Figure 3)

Characteristics of studies reporting the impact of anticoagulation on mortality in COVID-19 patients

Table 2 summarises the characteristics of the included studies reporting the impact of anticoagulation on mortality. Four studies were performed in Europe and the USA; only one was conducted in China. Although two studies evaluated the impact of pre-admission antithrombotic therapy, patients who discontinued antithrombotic drugs during hospitalisation were excluded. The number of COVID-19 patients ranged from 192 to 3,100. The mean age of the subjects ranged from 56 to 67 years, and the proportion of males ranged from 55% to 60%. Table S3 presents the quality assessment results.

Anticoagulation and risk of mortality in COVID-19 patients

This analysis included five studies (Ayerbe et al., 2020; Paranjpe et al., 2020; Russo et al., 2020; Tang et al., 2020; Tremblay et al., 2020), including 2886 and 5647 COVID-19 cases receiving and not receiving anticoagulants, respectively. Overall, the risk of mortality was similar between the anticoagulant-exposed and non-exposed COVID-19 patients (RR = 0.86, 95% CI, 0.69–1.09, P = 0.218; I^2 = 47.4%; Figure 2). Limiting the analysis to the studies providing adjusted data, there was no significant decrease in mortality risk in patients receiving anticoagulant therapy (RR = 0.84, 95% CI, 0.63–1.13, P = 0.243; I^2 = 57.6%). Excluding two studies that specified pre-admission antithrombotic therapy, the meta-analysis of the remaining three studies also found that anticoagulation was not associated with a lower risk of mortality (RR = 0.79, 95% CI, 0.48–1.31, P = 0.361; I^2 = 55.8%).

Discussion

Main findings

To our knowledge, this is the first systematic review and meta-analysis of the incidence of VTE and effects of anticoagulation on mortality in patients with COVID-19. We found that the overall rates of VTE, PE, and DVT were high (pooled incidence rates of 21%, 15%, and 27%, respectively). These rates were higher among patients admitted to the ICU, and antithrombotic therapy was not associated with a lower mortality risk.

Possible mechanisms underlying the findings

Although the relationship between SARS-CoV-2 and VTE was reported soon after the COVID-19 outbreak (Terpos et al., 2020; Wang et al., 2020), the underlying mechanism requires further

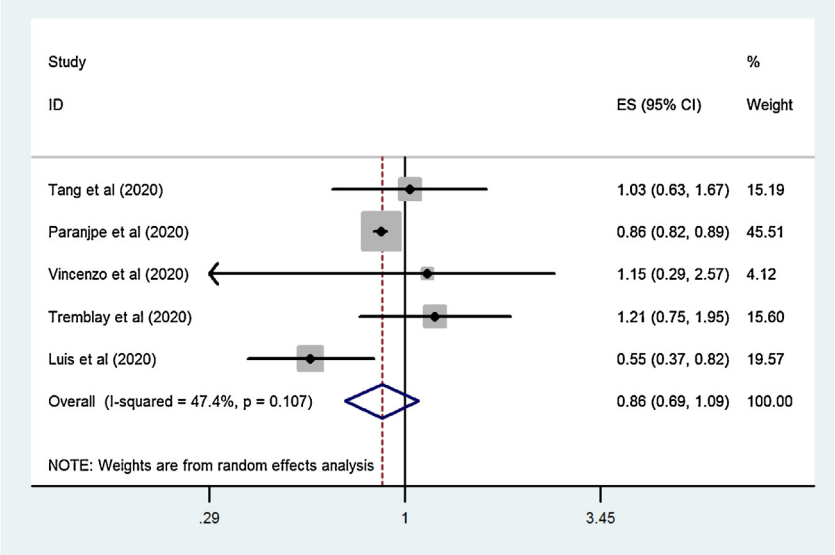

Figure 3. Forest plot of anticoagulation and risk of mortality in COVID-19 patients.

Table 2
Characteristics of the Included Studies.

Author	Country (city)	Study design	Study period	Age (year)	Male	Measurement of anticoagulant treatment	Anticoagulant	Non-anticoagulant	Confounder adjustment	Quality
Tang et al (2020)	China (Wuhan)	Single-center retrospective cohort	Jan 1 to Feb 13 2020	65.1 ± 12	60%	Medical record review	99	350	No	6
Paranjpe et al (2020)	USA (New York)	Multiple-center retrospective cohort	Mar 14 to Apr 11 2020	NA	NA	Medical record review	786	1987	Yes	8
Vincenzo et al (2020)	Italy (Lombardy region)	Multiple-center retrospective cohort	Feb to Apr 2020	67.7 ± 15.2	59.90%	Databases of health care use	26	166	Yes	6
Tremblay et al (2020)	USA (New York)	Multiple-center retrospective cohort	Mar 1 to Apr 1 2020	56.6 ± 18.2	55%	Databases of health care use	241	2859	Yes	8
Luis et al (2020)	Spain	Multiple-center retrospective cohort	to Apr 24 2020	67.6 ± 15.5	61%	Databases of health care use	1734	285	Yes	7

exploration. The first possible mechanism is cytokine storm caused by viral infection. Several studies have reported significantly higher plasma cytokine concentrations in COVID-19 patients than in healthy adults (Han et al., 2020; McGonagle et al., 2020; Wan et al., 2020). Furthermore, an elevated IL-6 level was associated with more severe COVID-19 infection (Han et al., 2020; Lagunas-Rangel and Chavez-Valencia, 2020). Inflammatory cytokines, such as TNF-α and IL-6, strongly induce the expression of tissue factors on endothelial cell surfaces and leucocytes, particularly monocytes (de Jonge et al., 2003; Mutlu et al., 2007). Tissue factors are the primary initiator of the blood coagulation cascade and strongly contribute to the hypercoagulable state in COVID-19 infection. Inflammatory cytokines can also trigger the release of ultra-large von Willebrand factor multimers from the endothelium (Tomaske et al., 2011), causing thrombotic microangiopathy; this has been confirmed at autopsy in patients who died from COVID-19(Ackermann et al., 2020). Finally, the concentrations of vascular heparin-like molecules are reduced by inflammation, which interferes with the natural anticoagulant pathways (Schmitt et al., 2019). The second potential mechanism is virus-induced endothelial dysfunction. SARS-CoV-2 is capable of directly infecting the vascular endothelium by entering cells via angiotensin-converting enzyme receptors (Zost et al., 2020), which results in the massive release of plasminogen activators and inhibition of fibrinolysis (Frantzeskaki et al., 2017). In SARS-CoV-1-infected patients, high plasma tissue-type plasminogen activator (t-PA) concentrations are observed (Giannis et al., 2020). The third putative mechanism is complement activation in viral pneumonia (Gralinski et al., 2018). Deposits of terminal complement components have been observed in the lungs of COVID-19 patients, indicating that dysregulated complement activation contributes to coagulopathy in COVID-19 patients (Magro et al., 2020). Other clinical factors, such as hypoxemia, hyperthermia, and hypovolemia, may also enhance the hypercoagulable state in COVID-19(55).

Unfortunately, our findings suggest that anticoagulation is unlikely to protect against COVID-19-related mortality. A previous meta-analysis (Zheng et al., 2020) demonstrated that cardiovascular diseases are related to an unfavourable prognosis in COVID-19 patients, so any investigation of the impact of anticoagulation on mortality should consider cardiovascular conditions. In our analysis, two studies (Russo et al., 2020; Tremblay et al., 2020) evaluated the impact of pre-admission antithrombotic therapy, which indicates underlying cardiovascular disease in the COVID-19 cases receiving anticoagulants. Therefore, the protective effect of anticoagulation may have been underestimated due to confounding by indication. However, further sensitivity analysis did not show a significant decrease in mortality in the COVID-19 patients who received antithrombotic therapy. Tang et al. (2020) observed that anticoagulant therapy appeared to be associated with a better prognosis in severe COVID-19 patients with markedly elevated D-dimer, implying that COVID-19 patients with other indications would benefit from anticoagulant therapy.

Implications for clinical practice

Our findings have important implications for clinicians. Hospitalised COVID-19 patients, particularly those admitted to the ICU, should have their coagulation function monitored through repeated measurements of D-dimer, prothrombin time, and platelet count. VTE should be suspected if patients have a high D-dimer or show rapid respiratory deterioration. The Padua or Caprini prediction score should be used to assess patients with mild symptoms of VTE; the use of standard-dose thromboprophylaxis is acceptable in hospitalized low-risk COVID-19 patients if they do not have medical contraindications. Furthermore, higher-dose VTE prophylaxis may benefit critically ill patients and seems to be associated with better outcomes.

Call for future studies

Considering the current controversies and challenges, more studies of COVID-19- coagulation are needed, including of the efficacy and safety of prophylactic and therapeutic anticoagulation. It is also necessary to develop a scoring system to estimate the risk of VTE in patients with COVID-19. Finally, the optimal dose of anticoagulant to prevent VTE in COVID-19 patients needs to be determined in controlled trials.

Strengths and limitations

The strengths of this meta-analysis included its compliance with the PRISMA statement and comprehensive search strategy. This review also had a major limitation with important implications regarding the interpretation of the results: it included a broad range of COVID-19 patients with widely varying characteristics. Moreover, the studies differed in terms of country of origin, definition of anticoagulant exposure, and design. These factors may have introduced heterogeneity, which could affect the results.

Conclusions

In summary, we reported a high pooled incidence of VTE and the need for coagulation monitoring in patients diagnosed with COVID-19. Additional high-quality data are needed to understand the risk of VTE, and the effects of anticoagulation on prognosis and mortality, in COVID-19 patients.

Authors' contributions

Y.F.L., L.Y.P., W.W.Z. and H.Y.J. conceived the study and revised the manuscript critically for important intellectual content. F.C. and S.S.H. made substantial contributions to its design, acquisition, analysis and interpretation of data. X.Z. participated in the design, acquisition, analysis and interpretation of data. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Ethical approve

No ethical approval was required for this review as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our review.

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