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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

Running title: COVID-19, VTE, and anticoagulation

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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.

Highlights

- The incidence of VTE among hospitalised COVID-19 patients was high, particular among patients in ICU.
- Anticoagulation was not associated with an increased risk of mortality in hospitalised COVID-19 patients.
- Clinical trials are urgently needed to evaluate the roles of prophylactic and therapeutic anticoagulation in COVID-19.

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; I² = 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.

**Keywords:** COVID-19; coagulation; antithrombotic; heparin.

**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(2), kidneys(3), and liver(4) that can lead to death.

Emerging data suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also targets the haematological system(5). Venous thromboembolic events (VTE) were reported in a case series of COVID-19 patients(6-8). In a very recent study(9), 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(10-29) 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 observational studies(30-34) 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 (1) the pooled incidence of VTE [PE or deep vein thrombosis (DVT)] in hospitalised patients with COVID-19 and (2) 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) 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: (1) case–control or cohort study; (2) no subjects in the reference group receiving anticoagulants; (3) odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) of subsequent mortality reported; (4) inclusion of adequate data to allow risk estimation; and (5) 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 ≥ 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, and statistical adjustments. The methodological quality was assessed using the Newcastle–Ottawa Scale (NOS)(35), 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(36). We used the I² statistic to assess statistical heterogeneity; an I² value > 50% was considered to indicate significant heterogeneity(37, 38). 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. Fig. 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 of males ranged from 52% to 81%. Table S2 presents the quality assessment results.

*VTE incidence*

Eleven studies (10, 11, 13, 15-17, 20-22, 26, 27) reported the overall incidence of VTE (ICU and general wards), which ranged from 4% to 42%. VTE occurred in 255 of 1,808 hospitalised patients. The meta-analysis revealed a pooled incidence rate of VTE of 21% (95% CI 15–27%, I² = 94.8%; Fig.2A) among all hospitalised patients. Eight(10, 13, 15, 16, 20-22, 27) 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%, I² = 92.4%; Fig.2B) among ICU patients.

Twelve studies(11, 12, 16-20, 22, 24, 26, 27) reported the overall incidence of PE, which varied from 2% to 35%. PE occurred in 238 out of 1,793 hospitalised patients. The meta-analysis revealed a pooled incidence rate of PE of 15% (95% CI 10% - 20%, I² = 93.5%; Fig.2C) among all hospitalised patients. Eight studies(12, 16, 18, 20-22, 24, 27) 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%, I² = 49.6%; Fig.2D) among ICU patients.

Nine studies(14, 16-18, 23-26, 28, 29) reported the overall incidence of DVT, which varied from 2% to 85%. DVT occurred in 212 out of 1,243 hospitalised patients. The meta-analysis revealed a pooled incidence rate of DVT of 27% (95% CI 19% - 36%, I² = 98.3%; Fig.2E) among all hospitalised patients. Seven studies(16, 18, 23-25, 28) 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%, I² = 98.8%; Fig.2F) among ICU patients.

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(30-34), including 2,886 and 5,647 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; I² = 47.4%; Fig.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; I² = 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; I² = 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(39, 40), the underlying mechanism requires further 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(41-43). Furthermore, an elevated IL-6 level was
associated with more severe COVID-19 infection(41, 44). Inflammatory cytokines, such as TNF-α and IL-6, strongly induce the expression of tissue factors on endothelial cell surfaces and leucocytes, particularly monocytes(45, 46). 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(47), causing thrombotic microangiopathy; this has been confirmed at autopsy in patients who died from COVID-19(48). Finally, the concentrations of vascular heparin-like molecules are reduced by inflammation, which interferes with the natural anticoagulant pathways(49).

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(50), which results in the massive release of plasminogen activators and inhibition of fibrinolysis(51). In SARS-CoV-1-infected patients, high plasma tissue-type plasminogen activator (t-PA) concentrations are observed(52). The third putative mechanism is complement activation in viral pneumonia(53). 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(54). 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(56) 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(32, 34) 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. (33) 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.

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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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| Author | Country (city) | Study design | Study period | Study site | Age (year) | Male | Outcomes | Number of COVID-19 case | 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 | French (Nantes) | Retrospective multi-center | Mar 25 to Apr 10 2020 | GW | 64 (46-75) | 60% | PE, DVT | 71 | 14 |
| Bompard et al, 2020 | French (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-Rodriguez 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 | French (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 | GW | 56 | 58.00% | PE, VTE, DVT | 61 | 14 |
| Study                  | Country         | Setting                          | Dates              | Setting  | ICU | DVT | PE, VTE | Number of Events | PE Rate | DVT Rate |
|------------------------|-----------------|----------------------------------|--------------------|----------|-----|-----|---------|------------------|---------|----------|
| Klok et al, 2020       | Netherlands (Paris) | Retrospective multi-center | Mar 7 to Apr 5 2020 | ICU      | 64  | 12  | 76%     | 184              | 18      | 18       |
| Leonard-Lorant et al, 2020 | French (Paris) | Retrospective multi-center | March 1 to 31 2020 | ICU and GW | 64  | 22  | 66%     | 106              | 14      | 14       |
| Llitjos et al, 2020    | French (Paris)  | Retrospective multi-center | Mar 19 to Apr 11 2020 | ICU    | 68  | 77% | PE, VTE | 26               | 13      | 13       |
| Lodigiani et al, 2020  | Italy (Milan)   | Retrospective single-center | Feb 13 to Apr 10 2020 | ICU    | 66  | 68% | PE, VTE, DVT | 388             | 16      | 16       |
| Middeldorp et al, 2020 | Netherlands (Amsterdam) | Retrospective single-center | Mar 2 to Apr 12 2020 | ICU and GW | 61  | 14  | 66%     | 198              | 16      | 16       |
| Nahum et al, 2020      | Germany (Nord)  | Retrospective single-center | Mar to Apr 2020    | ICU     | 62  | 78% | DVT     | 34               | 13      | 13       |
| Poissy et al, 2020     | French (Lille) | Retrospective single-center | Feb 27 to Mar 31 2020 | ICU | 57  | 59% | PE, DVT | 107             | 15      | 15       |
| Ren et al, 2020        | China (Wuhan)   | Retrospective single-center | Feb 27 to Mar 31 2020 | ICU     | 57  | 54% | DVT     | 48               | 10      | 10       |
| Author               | Country     | Study design                | Study period                     | Age (year) | Male | Measurement of anticoagulant treatment | Anticoagulant | Non-anticoagulant | Confounder adjustment | Quality |
|----------------------|-------------|-----------------------------|----------------------------------|------------|------|----------------------------------------|---------------|-------------------|-----------------------|---------|
| Stoneham et al, 2020 | UK (Brighton) | Retrospective multi-center  | Mar 20 to Apr 16, 2020           | NA         | NA   | PE, VTE, DVT                           | 274           | 16                |                       |         |
| Thomas et al, 2020   | UK (Cambridge) | Retrospective single-center | ICU and GW                      | 20-89      | NA   | PE, VTE                                | 63            | 14                |                       |         |
| Voicu et al, 2020    | French (Paris) | Prospective single-center  | ICU and GW                      | NA         | NA   | DVT                                    | 56            | 14                |                       |         |
| Zhang et al, 2020    | China (Wuhan) | Retrospective single-center | 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.

**Table 2** Characteristics of the Included Studies

- **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
| Study                          | Country          | Region             | Study Type                        | Dates            | Age Mean ± SD | Enrollment | Follow-up | Data Access | Study ID |
|-------------------------------|------------------|--------------------|-----------------------------------|------------------|---------------|------------|-----------|-------------|----------|
| Vincenzo et al, 2020          | Italy            | Lombardy region   | Multiple-center retrospective cohort | Feb to Apr 2020  | 67.7±15.2     | 166        | Yes       | 6           |
| Tremblay et al, 2020          | USA              | New York           | Multiple-center retrospective cohort | Mar 1 to Apr 1 2020 | 56.6±18.2     | 2859       | Yes       | 8           |
| Luis et al, 2020              | Spanish          | Multiple-center retrospective cohort | Mar 1 to Apr 1 2020 | 67.6±15.5     | 1734        | 285        | Yes       | 7           |
Fig.1 Flow chart of the studies considered and finally selected for review
**Fig. 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
Fig. 3 Forest plot of anticoagulation and risk of mortality in COVID-19 patients
Study ID ES (95% CI) Weight

Tang et al (2020) 1.03 (0.63, 1.87) 15.19
Paranjpe et al (2020) 0.68 (0.82, 0.39) 45.51
Vincenzo et al (2020) 1.15 (0.29, 2.57) 4.12
Tremblay et al (2020) 1.21 (0.75, 1.95) 15.60
Luis et al (2020) 0.55 (0.37, 0.82) 15.57
Overall (I-squared = 47.4%, p = 0.107) 0.88 (0.69, 1.09) 100.00

NOTE: Weights are from random effects analysis.