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Anticoagulation in COVID-19: A Systematic Review, Meta-analysis, and Rapid Guidance From Mayo Clinic

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Abstract

A higher risk of thrombosis has been described as a prominent feature of coronavirus disease 2019 (COVID-19). This systematic review synthesizes current data on thrombosis risk, prognostic implications, and anticoagulation effects in COVID-19. We included 37 studies from 4070 unique citations. Meta-analysis was performed when feasible. Coagulopathy and thrombotic events were frequent among patients with COVID-19 and further increased in those with more severe forms of the disease. We also present guidance on the prevention and management of thrombosis from a multidisciplinary panel of specialists from Mayo Clinic. The current certainty of evidence is generally very low and continues to evolve.

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Severe acute respiratory syndrome coronavirus (SARS-CoV) 2 causing coronavirus disease 2019 (COVID-19) has infected more than 5.5 million individuals worldwide and caused more than 350,000 deaths.[1] In the United States, there have been nearly 1.7 million confirmed cases and nearly 100,000 deaths.[1,2] A prominently described feature of this disease has been its hematologic manifestations and high risk of thrombosis. The COVID-19 laboratory signature includes lymphopenia, neutrophilia, and thrombocytopenia with elevated fibrinogen and fibrin degradation products (D-dimer). This signature is similar to that of previous coronavirus outbreaks including SARS-CoV-1 in China in 2002 and the Middle East respiratory syndrome coronavirus in 2012.[3-7] The International Society on Thrombosis and Haemostasis diagnostic criteria for overt disseminated intravascular coagulation (DIC)[8] included a category of coagulopathy associated with sepsis termed *sepsis-induced coagulopathy*.[9] Coagulopathy in SARS-CoV-2 has distinctive features including elevated fibrinogen levels with only modest thrombocytopenia despite marked elevations in fibrin D-dimer values, prompting some investigators to prefer the term *COVID-19–associated coagulopathy*. Thrombotic outcomes include an apparent increase in the incidence of venous thromboembolism (VTE). However, many questions remain regarding a true difference and

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contributing factors when compared with critically ill patients without COVID-19. In the intensive care unit (ICU) setting, VTE has often been described as occurring despite heparin prophylaxis and, in some cases, in the presence of therapeutic anticoagulation.

Although our understanding of the hematologic manifestations of COVID-19 remains in its early stages, this systematic review aims to provide a summary of current estimates of VTE risk, review anticipated laboratory values and their association with poor outcomes, discuss benefits and harms of anticoagulation, and provide suggestions for the prevention and management of this infection in patients who require hospitalization.

METHODS

The present review follows the recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10] and was designed to provide a description of coagulopathy and the role of anticoagulants in patients with COVID-19. The analytic framework is described in Figure 1. The review was conducted by the Mayo Clinic Evidence-based Practice Center.

Based on the evidence summarized in the systematic review, experts in thrombosis, pulmonary and critical care medicine, hematology, and cardiovascular medicine developed guidance for clinical practice. The guidance was achieved via consensus of this multidisciplinary group following critical review of the literature, available clinical experience, and serial discussions. This guidance is intended to help clinicians managing patients with COVID-19 in a large multistate health system.

Eligibility

We included primary studies—prospective and retrospective—in patients with COVID-19 that reported on at least one of the following: (1) frequency of coagulation abnormalities, (2) laboratory values of coagulation parameters, and (3) efficacy of pharmacological anticoagulation. We excluded

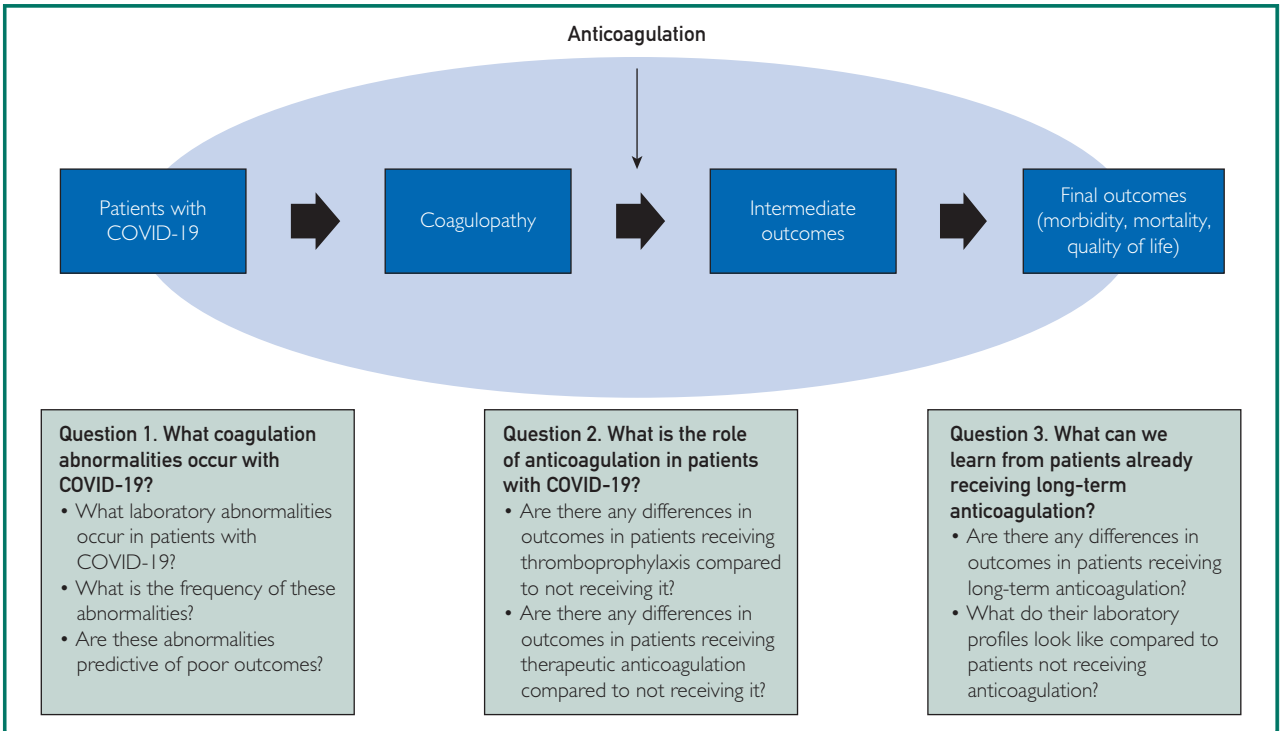

FIGURE 1. Analytic framework for the study. COVID-19 = coronavirus disease 2019.

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TABLE 1. Study Characteristics[a,b]

Reference, year	Study design, country	Setting	No. of patients	Target population	Population characteristics	Overall mortality
Beun et al,[13] 2020	Observational retrospective, Netherlands	ICU	75	Patients with COVID-19	100% Admitted to the ICU	Not reported
Cao et al,[21] 2020	Observational retrospective, China	Hospitalized	102	Patients with COVID-19	Patients aged 54±22.20 y, 48% female, 17.6% admitted to the ICU	16.7%
Chen et al,[22] 2020	Observational retrospective, China	Hospitalized	1590	Patients with COVID-19	Patients aged 48.7±15.80 y, 42% female, 6.22% admitted to the ICU	3.1%
Chen et al,[23] 2020	Observational retrospective, China	Hospitalized	203	Severely or critically ill patients with COVID-19	Patients aged 54±52.6 y, 46.8% female, 36% serious, 16.7% critical	12.8%
Gong et al,[24] 2020	Observational retrospective, China	Hospitalized	189	Patients with severe and nonsevere COVID-19	Patients aged 48±20.7 y, 53% female, 14.8% severe	Not reported
He et al,[25] 2020	Observational retrospective, China	Hospitalized	204	Patients with severe and nonsevere COVID-19	Patients aged 49±20.7 y, 61% female, 33.8% severe	12.7%
Klok et al,[14] 2020	Observational retrospective, Netherlands	ICU	184	Patients with COVID-19 who received thromboprophylaxis	Patients aged 64±12 y, 24% female, 9.2% in therapeutic anticoagulation at admission	13%
Léonard-Lorant et al,[26] 2020	Observational retrospective, France	Hospitalized	106	Patients who underwent CT including the chest for either suspicion or follow-up of COVID-19	Patients aged 63.3±17.31 y, 34% female, 30% admitted to the ICU, 39.6% on thromboprophylaxis at admission, 6.6% in therapeutic anticoagulation at admission	Not reported
Li et al,[27] 2020	Observational retrospective, China	Hospitalized	548	Patients with severe and nonsevere COVID-19	Patients aged 60±15.55 y, 49% female, 49.1% severe, 2.9% in therapeutic anticoagulation at admission	16.5%
Liu et al,[28] 2020	Observational retrospective, China	Hospitalized	383	Patients with COVID-19 with or without thrombocytopenia	Patients aged 46±4.5 y, 58% female	12.8%
Llitjos et al,[15] 2020	Observational retrospective, France	ICU	26	Patients with severe COVID-19 treated with prophylactic and therapeutic anticoagulation	Patients aged 68±17 y, 23% female, 31% on prophylactic anticoagulation, 69% on therapeutic anticoagulation	12%
Lodigiani et al,[29] 2020	Observational retrospective, Italy	Hospitalized	388	Patients with COVID-19	Patients aged 66±14.81 y, 32% female, 16% admitted to the ICU	26%
Fogarty et al,[16] 2020	Observational retrospective, Northern Ireland	ICU	83	Patients with COVID-19	Patients aged 62±16.3 y, 34% female, 27.7% admitted to the ICU, 5% in therapeutic anticoagulation at admission	15.7%

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TABLE 1. Continued

Reference, year	Study design, country	Setting	No. of patients	Target population	Population characteristics	Overall mortality
Panigada et al,[17] 2020	Observational retrospective, Italy	ICU	24	Patients with COVID-19	Patients aged 56±8 y	Not reported
Paranjpe et al,[30] 2020	Observational retrospective comparative (anticoagulation vs no anticoagu-lation), United States	Hospitalized	2773	Patients with COVID-19	Not reported	22.7%
Poissy et al,[18] 2020	Observational retrospective, France	ICU	107	Patients with COVID-19	Not reported	Not reported
Sun et al,[31] 2020	Observational retrospective, China	Hospitalized	150	Patients with COVID-19	Patients aged 45±16 y, 55% female	2%
Tang et al,[32] 2020	Observational retrospective, China	Hospitalized	183	Patients with COVID-19	Patients aged 54.1±16.2 y, 46% female	11.5%
Tang et al,[19] 2020	Observational retrospective, China	ICU	73	Patients with COVID-19	Patients aged 67±11.1 y, 38% female, 100% severe	28.8%
Tang et al,[33] 2020	Observational retrospective, China	Hospitalized	449	Patients with severe COVID-19	Patients aged 65.1±12 y, 40% female, 100% severe, 22% received anticoagulation	29.8%
Wan et al,[34] 2020	Observational retrospective, China	Hospitalized	230	Patients with COVID-19 with enteric involvement	Patients aged 47.5±13.83 y, 44% female, 26.5% severe, 15% admitted to the ICU	2.6%
Wan et al,[35] 2020	Observational retrospective, China	Hospitalized	123	Patients with COVID-19	Patients aged 46.16±15.15 y, 46% female, 17.07% severe	3.3%
Wan et al,[36] 2020	Observational retrospective, China	Hospitalized	135	Patients with severe and nonsevere COVID-19	Patients aged 47±3.1 y, 47% female, 29.6% severe	0.1%
Wang et al,[37] 2020	Observational retrospective, China	Hospitalized	125	Patients with critical and noncritical COVID-19	Patients aged 41.5±15.09 y, 43% female, 20% critical, 15.2% admitted to ICU	0%
Wang et al,[38] 2020	Observational prospective, China	Hospitalized	548	Patients with COVID-19	Patients aged 59.3±4.63 y, 49% female, 23.2% critical	14.2%
Wang et al,[20] 2020	Observational retrospective, China	ICU	344	Severely or critically ill patients with COVID-19	Patients aged 64±3.3 y, 48% female	36.7%
Wu et al,[39] 2020	Observational retrospective, China	Hospitalized	280	Patients with nonsevere, severe, and critical COVID-19	Patients aged 43.12±19.02 y, 46% female, 26.8% severe, 2.9% critical, 2.7% admitted to ICU	0%
Xu et al,[40] 2020	Observational retrospective, China	Hospitalized	187	Patients with nonsevere, severe, and critical COVID-19	Patients aged 62±16.67 y, 45% female, 24.1% severe, 33.2% critical, 33.2% admitted to ICU	14.9%
Yan et al,[41] 2020	Observational retrospective, China	Hospitalized	193	Patients with severe COVID-19 and diabetes	Patients aged 64±17.77 y, 41% female, 47.7% admitted to ICU	56%

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TABLE 1. Continued

Reference, year	Study design, country	Setting	No. of patients	Target population	Population characteristics	Overall mortality
Yang et al,[42] 2020	Observational retrospective, China	Hospitalized	1476	Patients with COVID-19	Patients aged 57±3.3 y, 47% female	16.1%
Yang et al,[43] 2020	Observational retrospective, China	Hospitalized	149	Patients with COVID-19	Patients aged 45.1±13.35 y, 46% female,	0%
Yao et al,[44] 2020	Observational retrospective, China	Hospitalized	109	Patients with severe and nonsevere COVID-19	Patients aged 52±3.5 y, 60% female, 23.1% severe, 15.74% admitted to ICU	11.1%
Yin et al,[45] 2020	Observational retrospective, China	Hospitalized	449	Patients with severe COVID-19	Patients aged 65.1±12 y, 40% female	29.8%
Peng et al,[46] 2020	Observational retrospective, China	Hospitalized	112	Patients with COVID-19 and cardiovascular disease	Patients aged 62±8.88 y, 53% female, 14.3% admitted to ICU	15.2%
Zhang et al,[47] 2020	Observational retrospective, China	Hospitalized	221	Patients with severe and nonsevere COVID-19	Patients aged 55±4.5 y, 51% female, 24.9% severe, 19.9 % admitted to ICU	5.4%
Zhang et al,[48] 2020	Observational retrospective, China	Hospitalized	343	Patients with COVID-19	Patients aged 62±15.5 y, 51% female, 1.2% had atrial fibrillation	3.8%
Zhou et al,[49] 2020	Observational retrospective, China	Hospitalized	191	Patients with COVID-19	Patients aged 56±15.6 y, 38% female, 26.2% admitted to the ICU	16.2%

[a]COVID-19 = coronavirus disease 2019; CT = computed tomography; ICU = intensive care unit.
[b]Continuous variables (eg, age) were summarized as mean ± SD.

studies with less than 100 participants that only reported the prevalence of coagulopathy without an intervention. Outcomes of interest were mortality, VTE, DIC, and major bleeding.

Literature Search and Data Extraction

The framework for conducting reviews about the COVID-19 pandemic has been published elsewhere.[11] A medical librarian and the methodology team designed a systematic search of Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, and Ovid EMBASE from the first outbreak in November, 2019, through May 1, 2020, without any language restrictions (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). We complemented the search by cross-referencing relevant systematic and rapid reviews identified by our search. Eight reviewers assessed each study for eligibility (V.D.T.R., T.N., M.U.S., S.S., R.B., M.F., T.J., M.A.), first by examining the abstracts and subsequently the full text of articles deemed potentially eligible. Both screening and data extraction were performed in a single-reviewer fashion.

We extracted study characteristics (eg, study design, setting) and population description (eg, target population, age range, number hospitalized vs ICU). Laboratory data were extracted as either binary (eg, presence of thrombocytopenia) or continuous using means and SDs. If not available, SDs were imputed from interquartile ranges. The number of reported VTE and DIC events was also extracted. Severity of disease was categorized as mild, moderate, severe, or critical according to the description provided in each publication. Mild disease includes low-grade fever ($<38^{\circ}C$) with few symptoms and no imaging findings of pneumonia. Moderate disease includes fever, respiratory symptoms, and imaging features of pneumonia. Severe disease includes evidence of respiratory distress (respiratory rate $\geq$30 breaths/min, oxygen saturation $<$93% at rest, PaO_2/fraction of inspired oxygen $\leq$300 mm Hg); critical disease severity includes respiratory failure with the need for mechanical assistance, shock, and/or extrapulmonary organ failure requiring ICU management.[12] The system of disease severity, however, may not have been consistent across publications.

Information regarding reporting related to risk of bias at study level was extracted separately for comparative and single-arm studies (Supplemental Tables 2 and 3, available online at http://www.mayoclinicproceedings.org). Domains evaluated include representativeness of the cohorts, ascertainment of exposure and outcomes, comparability, causality, reporting, and loss of follow-up.

Data Synthesis

When feasible, we conducted meta-analysis using the DerSimonian-Laird random effects model to calculate an overall proportion or a summary estimate of means. Heterogeneity was assessed using the I^2 value, defining low heterogeneity as I^2 lower than 50%, moderate heterogeneity as I^2 between 50% and 75%, and high heterogeneity as I^2 higher than 75%. We used the open-source R Project software for all statistical computing. We opted to divide patients with mild and moderate disease from those with severe and critical disease. Similarly, we compared the data of survivors to nonsurvivors. We then calculated odds ratios (ORs) and 95% CIs to evaluate the association of severity and survivorship with coagulopathy using binary data. When meta-analysis was not possible, data were synthesized narratively.

RESULTS

Study Characteristics

Of the 4070 unique citations identified, we included 37 studies (Table 1). Of these studies, 36 were retrospective studies; 8 were conducted in the ICU setting,[13,14,15,16,17,18,19,20] 29 in nonspecific inpatient settings,[21–25,26–28,29,30,31,32,33–38,39–49] and none in an outpatient setting. The studies were from 6 countries with the majority (28 of 37) from China, followed by France (3), Italy (2), the Netherlands (2), Ireland (1), and the United States (1). Cohorts ranged from 24 to 2773 patients with confirmed

TABLE 2. Laboratory Findings[a,b,c]

Laboratory findings	Frequency	Overall	Patients with mild and/or moderate disease	Patients with severe and/or critical disease	Survivors	Nonsurvivors
PT (s) Reference value: 10-12 s	Prolonged PT in **7%** (95% CI, 1%-14%) 5 Studies,[17,31,37,43,49] 639 patients, high heterogeneity	Mean: **12.97** (95% CI, 12.41-13.54) 16 Studies,[25,16,19,31,32,36,37,20,39–41,43,45-48] high heterogeneity	Mean: **12.51** (95% CI, 11.79-13.24) 6 Studies,[25,32,36,39,46,47] high heterogeneity	Mean: **13.27** (95% CI, 12.57-13.97) 8 Studies,[25,19,36,20,39,41,46,47] high heterogeneity	Mean: **13.22** (95% CI, 12.64-13.80) 4 Studies,[16,32,20,40] high heterogeneity	Mean: **14.32** (95% CI, 13.02-15.61) 4 Studies,[16,32,20,40] high heterogeneity
aPTT (s) Reference value: 22-36 s	Prolonged aPTT in **11%** (95% CI, 0% to 34%) 3 Studies,[17,37,43] 298 patients, high heterogeneity	Mean: **34.43** (95% CI, 32.06-36.8) 13 Studies,[24,16,32,19,34,36,37,39,41,43,46-48] high heterogeneity	Mean: **35.69** (95% CI, 32.74-38.64) 6 Studies,[24,32,36,39,46,47] high heterogeneity	Mean: **36.94** (95% CI, 34.70-39.19) 7 Studies,[24,19,36,39,41,46,47], high heterogeneity	Mean: **36.26** (95% CI, 26.56-45.96) 2 Studies,[16,32] high heterogeneity	Mean: **37.60** (95% CI, 26.56-45.96) 2 Studies,[16,32] high heterogeneity
Fibrinogen (g/L) Reference value: 2-4 g/L	Not reported	Mean: **5.29** (95% CI, 4.76-5.81) 9 Studies,[13,26,28,15,16,17,32,41,48] high heterogeneity	Mean: **4.55** (95% CI, 4.51-4.59) 1 Study[32]	Mean **6.29** (95% CI, 4.58-7.99) 4 Studies,[13,15,17,41] high heterogeneity	Mean: **4.51** (95% CI, 4.47-4.55) 2 Studies,[16,32] low heterogeneity	Mean: **5.30** (95% CI, 4.90-5.71) 2 Studies,[16,32] low heterogeneity
D-dimer (μg/mL) Reference value: <0.5 μg/mL	Elevated D-dimer in **42%** (95% CI, 28%-55%) 13 Studies,[21–23,26,27,31,36–38,43,44,48,49] 3454 patients, high heterogeneity	Mean: **0.56** (95% CI, 0.49-0.63) 26 Studies,[13,21,23–25,26,15–17,28,29,19,31,32,34,36,37,20,39–41,43-45,47,48] high heterogeneity	Mean: **0.48** (95% CI, 0.24-0.72) 7 Studies,[24,25,32,36,39,44,47] high heterogeneity	Mean: **1.29** (95% CI, 0.72-1.86) 13 Studies,[13,23–25,15,17,19,36,20,39,41,44,47] high heterogeneity	Mean: **0.70** (95% CI, 0.53-0.88) 7 Studies,[23,29,16,32,20,40,44] high heterogeneity	Mean: **1.10** (95% CI, 0.50-1.69) 8 Studies,[21,23,29,16,32,20,40,44] high heterogeneity
Antithrombin activity (%) Reference value: 80%-140%	Not reported	Mean: **91** (95% CI, 90.7-91.3) 1 Study[32]	Not reported	Not reported	Mean: **91** (95% CI, 90.7-91.3) 1 Study[32]	Mean: **84** (95% CI, 82.-85.3) 1 Study[32]
Platelets ($\times 10^9$/L) Reference value: 150-400 $\times$ 10^9/L	Thrombocytopenia in **20%** (95% CI, 9%-33%) 10 Studies,[22,23,27,17,35,37,38,42-44] 4894 patients, high heterogeneity	Mean: **186.20** (95% CI, 161.22-211.18) 19 Studies,[13,23–25,28,15,16,17,19,36,37,20,39,41-43,45,47,49] high heterogeneity	Mean: **184.70** (95% CI, 172.84-196.56) 6 Studies,[24,25,36,37,39,47] moderate heterogeneity	Mean: **177.30** (95% CI, 141.93-212.67) 13 Studies,[13,23–25,15,17,19,36,37,20,39,41,47] high heterogeneity	Mean: **205.82** (95% CI, 190.37-221.27) 5 Studies,[23,16,20,42,49] low heterogeneity	Mean: **146.71** (95% CI, 113.07-180.35) 5 Studies,[23,16,20,42,49] high heterogeneity
Lymphocytes ($\times 10^9$/L) Reference value: 1.1-3.2 $\times 10^9$/L	Not reported	Mean: **1.14** (95% CI, 1.04-1.25) 19 Studies,[21,23–25,28,31,19,34,36,37,20,39–41,43,44,46,47,49] high heterogeneity	Mean: **1.21** (95% CI, 1.07-1.34) 8 Studies,[24,25,36,37,39,44,46,47] high heterogeneity	Mean: **0.79** (95% CI, 0.69-0.89) 11 Studies,[23–25,19,36,37,20,39,41,44,46,47] high heterogeneity	Mean: **0.92** (95% CI, 0.81-1.04) 5 Studies,[23,20,40,44,49] high heterogeneity	Mean: **0.62** (95% CI, 0.55-0.70) 6 Studies,[21,23,20,40,44,49] moderate heterogeneity

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TABLE 2. Continued

Laboratory findings	Frequency	Overall	Patients with mild and/or moderate disease	Patients with severe and/or critical disease	Survivors	Nonsurvivors
Neutrophils ($\times 10^9$/L) Reference value: 3.8-9.5 $\times 10^9$/L	Not reported	Mean: **3.59** (95% CI, 2.91-4.27) 17 Studies,[23–25,28,31,19,34,36,37,20,39–41,43,44,46,47] high heterogeneity	Mean: **3.16** (95% CI, 2.87-3.45) 8 Studies,[24,25,36,37,39,44,46,47] high heterogeneity	Mean: **4.19** (95% CI, 3.3-5.09) 11 Studies,[23–25,19,36,37,20,39,41,44,46,47] high heterogeneity	Mean: **3.95** (95% CI, 3.76-4.14) 4 Studies,[23,20,40,44] low heterogeneity	Mean: **6.11** (95% CI, 5.68-6.55) 4 Studies,[23,20,40,44] low heterogeneity

[a]aPTT = activated partial thromboplastin time; PT = prothrombin time.
[b]Heterogeneity was assessed using the I^2 value, defining low heterogeneity as I^2 <50%, moderate heterogeneity as I^2 50%-75%, and high heterogeneity as I^2 >75%. We used the open-source R Project software for all statistical computing.
[c]SI conversion factors: To convert D-dimer values to nmol/L, multiply by 5.476.

COVID-19. Overall mortality was as high as 56%. We found no studies reporting data on patients who were receiving long-term anticoagulation.

Laboratory Findings

Eight laboratory parameters were described by at least one study with sufficient detail to calculate means and 95% CIs (Table 2). The reported frequency of abnormal coagulation parameters was as follows: elevated D-dimer, 42%; coagulopathy (prolongation of either prothrombin time [PT] or activated thromboplastin time [aPTT]), 28%; thrombocytopenia, 20%; prolonged aPTT, 11%; and prolonged PT, 7%.

The coagulopathy in COVID-19 differed from DIC in that fibrinogen levels are elevated (in classic DIC, they should be low and are often <1 g/L), thrombocytopenia is mild (platelet counts in DIC are usually $<50 \times 10^9$/L)[50] and the PT is only slightly prolonged (1 to 2 seconds vs 3 to >6 seconds in DIC due to consumption of procoagulant factors).

Prognosis

During hospitalization, patients with severe and critical forms of COVID-19 were more likely to have elevation of D-dimer levels of greater than 1 μg/mL (to convert to nmol/L, multiply by 5.476) (OR, 3.14; 95% CI, 2.26 to 4.38; 2 studies, I^2=0%) and thrombocytopenia (OR, 1.78; 95% CI, 1.18 to 2.69; 3 studies, I^2=9%) compared with patients with mild or moderate disease. Nonsurvivors were more likely to have elevation of D-dimer values (OR, 4.78; 95% CI, 2.47 to 9.25; 4 studies, I^2=66%), thrombocytopenia (OR, 4.56; 95% CI, 1.09 to 19.09; 4 studies, I^2=96%), and DIC (OR, 71.88; 95% CI, 3.42 to 1508.54; 2 studies, I^2=86%).

Incidence of Thrombotic Events and Comparison With Non-COVID Patients

Published series were largely drawn from patients with COVID-19 who were admitted to the ICU. Venous thromboembolism rates ranged from 2% to 69% based on 3 published studies at the time of this analysis.

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This wide range reflects differing detection strategies, potentially limited by personal protective equipment conservation tactics. In studies in which ultrasonography was prompted by clinical suspicion alone, reported VTE rates were low at 2% to 4%.[14,29] In the only study in which surveillance ultrasonography was mandated, the VTE rate was 69%.[15] The latter study pursued mandatory ultrasonography on admission and repeated on day 7 and reported a deep venous thrombosis (DVT) rate of 50%, most of which were bilateral lower extremity DVTs; however, the rates of proximal and distal thromboses were not reported.[15] In a retrospective case series by Cui et al[51] in which 81 patients with COVID-19 were admitted to the ICU, the VTE rate was 25%. This series did not meet the eligibility criteria for inclusion in this review because of its sample size; however, it reports a high VTE incidence. This study included ultrasonography and computed tomography that may not have been mandatory and may not have been repeated as described in the article's Methods section.

The incidence of VTE in these 2 studies was considerably higher than anticipated for ICU patients. By comparison, VTE rates in the PROTECT (Prophylaxis for Thromboembolism in Critical Care Trial) study (pre−COVID-19) were substantially lower: the overall VTE rate was 9.1%, the DVT rate was 5.5%, and the pulmonary embolism (PE) rate was 1.8%.[52] The PROTECT study randomized 3764 ICU patients to receive either prophylactic low-molecular-weight heparin (LMWH), dalteparin, or unfractionated heparin to be continued throughout the ICU stay. Patients underwent mandatory ultrasonographic evaluation of the lower extremities twice weekly for DVT. Nearly half of the recruited patients (45%) were admitted for a respiratory condition. Proximal leg DVT was identified in 5.1% and 5.8% of patients, while PE rates were 1.3% and 2.3% for patients receiving dalteparin and unfractionated heparin, respectively.

One study reported rates of VTE in patients with COVID-19 hospitalized in a non−critical care setting.[29] Overall, thrombosis rates were 6.6% for 327 non-ICU patients.[29] This rate includes VTE rates of 3.8%, stroke rates of 1.9%, and acute coronary syndrome rates of 1.0%. Of the 3.8% of patients with VTE, PE occurred in 2.5% and DVT in 1.3%. It is important to note that DVT detection methods were driven by clinical indications, not systematic ultrasonographic surveillance requirements.

When looking at differences by disease severity, one study found higher rates of thrombosis among patients with severe COVID-19 than in those with nonsevere disease (6.6% vs 3.7%) but found no difference in DVT or PE rates.[29] Moreover, PE rates in studies in which more than 50% of patients had severe or critical disease[13,14,15,18] ranged from 13.6% to 26.7% compared with 1.4% to 30.2% in studies in which less than 50% of patients had severe or critical disease[26,29] (Table 3).

In 2 studies in which more than 50% of patients received prophylaxis, rates of VTE ranged from 1.6% to 4.1%[14,29] and PE rates ranged from 1.4% to 20.6%,[14,29,18] whereas in studies with less prophylaxis, the VTE rate was 69%[15] and PE rates ranged from 23.1% to 30.2%.[26,15] Meta-analyses of the frequency of thrombotic events are summarized in Table 3, ranging from 1% (myocardial infarction) to 17% (PE). Each pooled analysis included 2 to 6 studies with sample sizes of 598 to 1362 patients. Overall heterogeneity was moderate to high. An overall VTE rate was not pooled across studies because of high heterogeneity.

Effect of Anticoagulation

Six retrospective studies (4 comparative[15,30,33,45] and 2 uncontrolled[14,29]) reported patient-important outcomes in those who received anticoagulation (Table 4). Two of the comparative studies reported data from the same cohort.[33,45] Mortality was assessed by 2 comparative studies,[30,33,45] meta-analysis of which did not reveal a statistically significant difference when using anticoagulation (OR, 0.99; 95% CI, 0.82 to 1.19; I^2=0%). In one cohort study,[45] patients with D-dimer levels greater than 3.0 μg/mL treated with

TABLE 3. Incidence of Thrombotic Events[a,b]

Reference, year	Severity	Use of anticoagulants	VTE	DVT	PE	Stroke	MI	DIC
Klok et al,[14] 2020 (N=184)	100% Critical or severe	100% Received prophylaxis	All participants: 1.6%	All participants: 0%	All participants: 13.6%	All participants: 1.6%	NR	NR
Llitjos et al,[15] 2020 (N=26)	100% Critical or severe	31% Received prophylaxis at admission 69% Received therapeutic anticoagulation	All participants: 69%	All participants: 50%	All participants: 23.1%	NR	NR	NR
Lodigiani et al,[29] 2020 (N=388)	15.7% Critical or severe	79.1% Received prophylaxis 19.6% Received therapeutic anticoagulation	All participants: 4.1% Mild or moderate: 3.7% Critical or severe: 6.6%	All participants: 1.4% Mild or moderate: 1.2% Critical or severe: 1.6%	All participants: 1.4% Mild or moderate: 1.2% Critical or severe: 1.6%	All participants: 2.3% Mild or moderate: 1.8% Critical or severe: 4.9%	All participants: 1.0% Mild or moderate: 0.9% Critical or severe: 1.6%	NR
Poissy et al,[18] 2020 (N=107)	100% Critical or severe	90.9% of patients with PE were receiving prophylaxis	NR	All participants: 4.7%	All participants: 20.6%	NR	NR	NR
Beun et al,[13] 2020 (N=75)	100% Critical or severe	NR	NR	All participants: 4%	All participants: 26.7%	All participants: 2.7%	NR	NR
Léonard-Lorant et al,[26] 2020 (N=106)	30% Critical or severe	39.6% Received prophylaxis at admission 6.6% Received therapeutic anticoagulation at admission	NR	NR	All participants: 30.2%	NR	NR	NR
Sun et al,[31] 2020 (N=150)	26% Critical or severe	NR	NR	NR	NR	1.3%	NR	NR
Chen et al,[23] 2020 (N=203)	52.7% Critical or severe	NR	NR	NR	NR	NR	All participants: 1.5%	NR
Tang et al,[32] 2020 (N=183)	NR	NR	NR	NR	NR	NR	NR	All participants: 8.7% Survivors: 0.6% Nonsurvivors: 71.4%

Continued on next page

TABLE 3. Continued

Reference, year	Severity	Use of anticoagulants	VTE	DVT	PE	Stroke	MI	DIC
Wang et al,[38] 2020 (N=548)	23.2% Critical	NR	NR	NR	NR	NR	NR	All participants: 7.7% Survivors: 3.0% Nonsurvivors: 35.9%
Fogarty et al,[16] 2020 (N=83)	40% Critical or severe	100% Received prophylaxis 4.8% Received anticoagulation therapy	NR	NR	NR	NR	NR	All participants: 0.0%
Li et al,[27] 2020 (N=548)	50.9% Critical or severe	2.9% Received therapeutic anticoagulation	NR	NR	NR	NR	NR	All participants: 7.7% Mild or moderate: 1.8% Critical or severe: 13.8%
Pooled analysis	NA	NA	N=598 **2%-69%** 3 Studies, high heterogeneity	N=754 **2%** (95% CI, 0%-5%) 4 Studies, moderate heterogeneity	N=886 **17%** (95% CI, 6%-33%) 6 Studies, high heterogeneity	N=797 **2%** (95% CI, 1%-3%) 4 Studies, low heterogeneity	N=591 **1%** (95% CI, 0%-2%) 2 Studies, low heterogeneity	N=1362 **6%** (95% CI, 3%-9%) 4 Studies, high heterogeneity

[a]DIC = disseminated intravascular disease; DVT= deep venous thrombosis; MI = myocardial infarction; NA = not applicable; NR = not reported; PE = pulmonary embolism; VTE= venous thromboembolism.
[b]Heterogeneity was assessed using the I^2 value, defining low heterogeneity as I^2 <50%, moderate heterogeneity as I^2 50%-75%, and high heterogeneity as I^2 >75%. We used the open-source R Project software for all statistical computing. We opted not to pool the overall rate of VTE because of the high heterogeneity due to screening practices.

unfractionated heparin had lower mortality than those not receiving unfractionated heparin (32.8% vs 52.4%; P=.02). Higher risk of VTE was also associated with the need for mechanical ventilation[30] in patients receiving anticoagulants. In one study,[15] VTE rates were significantly higher for patients receiving prophylaxis-dosed anticoagulants compared with therapeutic-dosed anticoagulation (100% vs 56%; P=.03). The small sample size of this study, however, limits the interpretation of these findings. Indeed, the certainty of evidence in all outcomes of anticoagulation is rated as very low, considering the observational nature of the studies and their small size leading to important imprecision.[53] Risk of bias is described in Supplemental Tables 2 and 3.

EXPERT CONSENSUS: SUGGESTED APPROACH

Prevention of Thrombosis

The following approach to patients requiring hospitalization for COVID-19–related complications is suggested (Figure 2). First, it should be determined whether the patient is already receiving therapeutic anticoagulation for a well-defined indication. For such patients, transitioning to parenteral anticoagulation, such as unfractionated heparin or LMWH, should be considered particularly if an invasive procedure is anticipated. This transition will facilitate prompt and efficient scheduling with timely pursuit of these procedures in an otherwise ill patient.

Second, for patients not receiving therapeutic anticoagulants, it is then important to determine which form of VTE prophylaxis is most appropriate. This determination will require an assessment of bleeding risk. For patients with active bleeding, severe thrombocytopenia (platelet count $<25 \times 10^9$/L), or an underlying congenital bleeding disorder, nonpharmacological prophylaxis with sequential compression devices should be initiated. Once bleeding resolves with certainty, platelet counts recover, or the appropriate management of the underlying congenital bleeding disorder is addressed, pharmacological prophylaxis can again be reconsidered. Guideline recommendations state a preference for enoxaparin (an LMWH) prophylaxis at a dose of 40 mg subcutaneously (SC) daily for all hospitalized patients provided there are no contraindications.[54,55] For patients with a body mass index (calculated as weight in kilograms divided by height in meters squared) exceeding 40 kg/m^2 or actual body weight greater than 120 kg, the enoxaparin dose of 40 mg SC twice daily should be considered. For patients with renal impairment (creatinine clearance <30 mL/min), unfractionated heparin at doses of 5000 U SC twice daily or 3 times daily is reasonable. For patients with a history of heparin-induced thrombocytopenia and acceptable renal function (creatinine clearance ≥30 mL/min), fondaparinux at 2.5 mg SC once daily can be used. Careful daily clinical assessment for signs or symptoms of VTE should be employed, with a low threshold for imaging in the presence of clinical findings. Given the 8.3% incidence of VTE for patients on hospital wards reported by Lodigiani et al,[29] these recommendations strike a reasonable balance between VTE prevention and bleeding. It is noteworthy that reports of excessive bleeding in COVID-19–infected patients residing in the hospital have not been published. Two groups with patients receiving anticoagulants reported bleeding rates of 0% to 3%.[29,30]

Third, baseline laboratory assessment should include a complete blood cell count with differential, PT/aPTT, fibrinogen, and D-dimer assessment. Because trends in platelet counts and fibrin D-dimer values have prognostic implications, repeating these measures periodically, particularly for the ICU patient, can be informative.[22,23,38,42,49] These trends must be interpreted in the context of the overall clinical picture including other important prognostic variables. For patients with prolonged PT or aPTT, more detailed coagulation testing should be pursued to exclude lupus anticoagulant or factor deficiency.

Fourth, a distinction between patients requiring medical care in hospital wards from those requiring ICU care should be considered. For the patient requiring admission to the ICU, baseline screening leg

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TABLE 4. Studies Reporting on Anticoagulation[a,b]

Reference, year	Design	Type of anticoagulation and comparison	Outcomes reported	Results
Tang et al,[33] 2020	Comparative, retrospective, 449 patients	Systemic anticoagulation with low-molecular-weight heparin vs no anticoagulation	Mortality	No difference was observed in mortality (30.3% vs 29.7%; *P*=.91)
Paranjpe et al,[30] 2020	Comparative, retrospective, 2772 patients	Systemic anticoagulation vs no anticoagulation	Mortality, major bleeding, mechanical ventilation requirement	No difference in mortality (22.5% vs 22.8%) or bleeding (1.9% vs 3%; *P*=.2). Patients on anticoagulation required more mechanical ventilation (29.8% vs 8.1%; *P*<.001)
Llitjos et al,[15] 2020	Comparative, retrospective, 26 patients	Thromboprophylaxis vs therapeutic anticoagulation	VTE	Patients treated with thromboprophylaxis were at higher risk of VTE (100% vs 56%; *P*=.03)
Yin et al,[45] 2020	Comparative, retrospective, 449	Systemic anticoagulation with low-molecular-weight heparin vs no anticoagulation	Mortality	No difference was observed in mortality (30.3% vs 29.7%; *P*=.91). In subgroup analysis of patients with D-dimer >3.0 μg/mL, there was lower risk of mortality in the heparin group (32.8% vs 52.4%; *P*=.02)
Klok et al,[14] 2020	Single-arm, retrospective, 184 patients	Thromboprophylaxis	Any thromboembolic event, PE	Any thromboembolic event occurred in 31% of patients. PE occurred in 13.6% of patients
Lodigiani et al,[29] 2020	Single-arm, retrospective, 61 patients	Thromboprophylaxis	Any thromboembolic event, VTE, PE, DVT, stroke	Thromboembolic events occurred in 16.7% of patients, VTE in 8.3%, PE in 4.2%, DVT in 2.1%, and stroke in 6.3%

[a]DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
[b]SI conversion factors: To convert D-dimer values to nmol/L, multiply by 5.476.

ultrasonography on admission to exclude incident DVT should be considered. Given the differing DVT rates of ICU patients in published studies, this recommendation does not appear to be excessive and will identify subclinical DVT in a sizable percentage of patients (Table 3). For individuals with identified DVT, therapeutic anticoagulation management will be initiated. If ultrasonographic findings are normal, ICU patients should be further assessed for VTE risk using fibrin D-dimer levels. Tang et al[33] found that fibrin D-dimer levels exceeding 6 times the upper limit of normal identified a high-risk population who benefited from aggressive VTE prophylaxis with a survival benefit. Low-risk ICU patients should receive enoxaparin, 40 mg SC daily or twice daily depending on body weight. For those with renal impairment (creatinine clearance <30 mL/min), unfractionated heparin adjusted for body weight should be prescribed. A daily clinical assessment for VTE signs and symptoms and a low threshold for imaging confirmation is advisable. Upper extremity ultrasonography should be considered particularly for patients with arm swelling and a central venous catheter. Based on the work by Llitjos et al,[15] weekly ultrasonographic

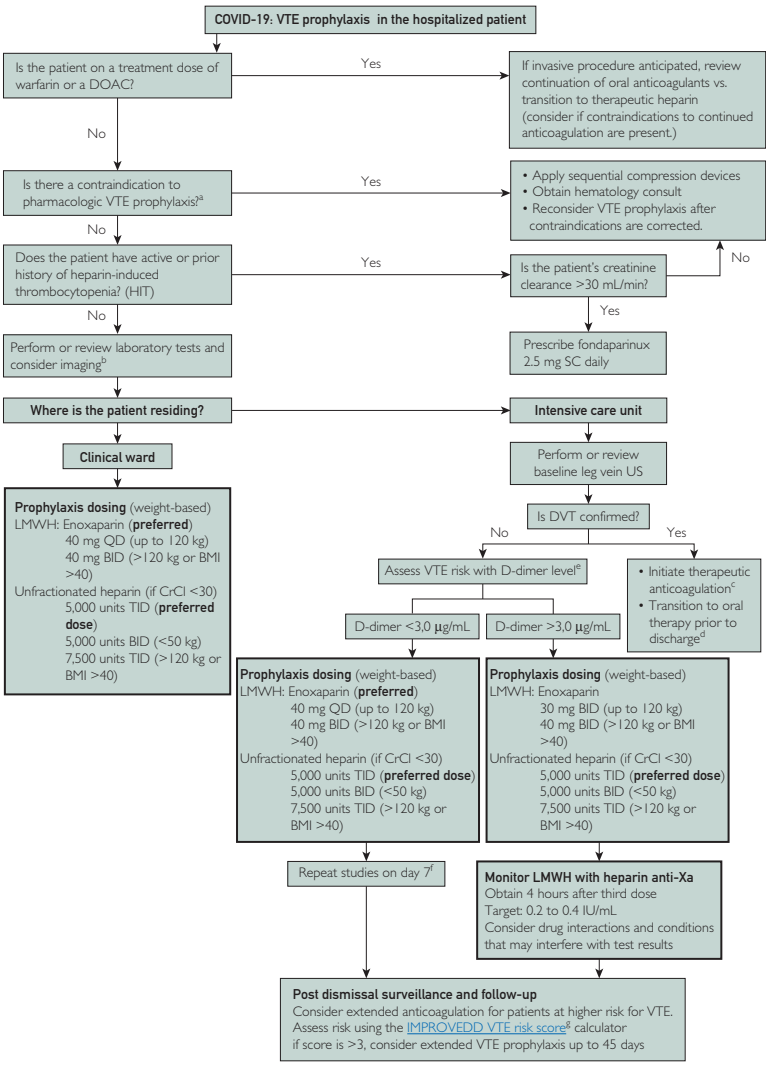

FIGURE 2. Suggested approach to patients requiring hospitalization for coronavirus disease 2019 (COVID-19)–related complications. [a]Active bleeding, platelet count $<30 \times 10^9$/L, or congenital bleeding disorder including von Willebrand disease or hemophilia. [b]Laboratory tests: complete blood cell count and differential, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer. If PT and/or aPTT are prolonged, consider a special coagulation profile, which includes a lupus anticoagulant screen. Imaging: for patients presenting with a prolonged illness or those who have had a long hospital stay, consider obtaining bilateral lower extremity venous ultrasonography. [c]Initiate therapeutic anticoagulation therapy as follows: unfractionated heparin infusion is preferred; in a patient with a history of heparin-induced thrombocytopenia, use argatroban or bivalirudin (see direct thrombin inhibitors order set). [d]Continue oral anticoagulation for a minimum of 3 months with clinical reassessment thereafter. A direct oral anticoagulant (DOAC) is preferred unless the patient has another indication for the use of a vitamin K antagonist or low-molecular-weight heparin (LMWH). [e]Assess venous thromboembolism (VTE) risk using the D-dimer level as follows: low risk, <3.0 µg/mL; high risk, 3.0 µg/mL. This recommendation reflects a 6-fold increase above the upper limit of normal. Precise cutoff requires external validation. [f]On day 7 of therapy (or earlier if clinical deterioration occurs), repeat the following studies: bilateral lower extremity venous ultrasonography; laboratory tests (complete blood cell count with differential, D-dimer, and fibrinogen). Consider alternating ultrasonography and laboratory tests every 3 to 4 days.

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surveillance for leg DVT in the ICU may identify patients with subclinical thrombotic events that will impact management. For high-risk patients with D-dimer values exceeding 3.0 μg/mL, a more aggressive approach to VTE prophylaxis should be considered with enoxaparin, 30 mg twice daily for those with body weight of 120 kg of less (body mass index ≤40) and 40 mg twice daily for heavier patients. For these high-risk patients, prophylaxis should be monitored with a heparin anti-Xa level obtained 4 hours after the third dose targeting levels of 0.2 to 0.4 IU/mL.[33] In addition, daily clinical assessment for VTE signs and symptoms, a low threshold for imaging any new clinical findings, and weekly ultrasonographic surveillance for leg DVT while in the ICU is recommended. For patients with severe renal impairment (creatinine clearance <30 mL/min), unfractionated heparin at doses of 5000 U SC 3 times daily is a reasonable alternative. Consider including weekly ultrasonographic surveillance of upper extremities if intravenous catheter is in place to evaluate for catheter-associated thrombosis.

Following hospital dismissal, there has been interest in extending VTE prophylaxis to the outpatient setting.[54] These recommendations are largely driven by recent direct oral anticoagulant (DOAC) trials with apixaban, betrixaban, and rivaroxaban in non−COVID-19 populations.[56-58] Extending prophylaxis to 35 to 45 days after hospital discharge may reduce venous thrombotic events while slightly increasing bleeding events. Decision making requires a careful balance between these 2 outcomes to maximize net clinical benefit for these patients. Although there are no current data on extended prophylaxis for COVID-19, this approach may be beneficial for patients recovering from pulmonary manifestations of this infection,[59] especially those who are less mobile. There are several risk assessment tools that can be utilized to help identify high-risk patients who may benefit from extended prophylaxis.[60,61]

Treatment of Thrombosis

If VTE is identified, we suggest initiating therapy with parenteral anticoagulants. These patients should be managed with the same principles and practices used to manage patients without COVID-19.[62] Once stabilized, patients can be transitioned to oral anticoagulant therapy, which could include either a DOAC or vitamin K antagonist depending on patient-specific variables. Duration of anticoagulant therapy will vary with patient-specific circumstances including perceived ongoing risk factors and potential indications for long-term anticoagulation (eg, atrial fibrillation). In general, a minimum treatment duration of 3 months of therapeutic anticoagulation should be considered. Although thrombophilia testing would not be indicated for most patients with confirmed VTE, lupus anticoagulant testing may be considered for those individuals with prolonged clotting times (particularly aPTT). If lupus anticoagulant is identified, enzyme-linked immunosorbent assay for anticardiolipin and β_2-glycoprotein 1 antibodies should also be obtained for completeness. These assays should also be repeated in 12 weeks to determine persistence. There have been concerns that patients may have progressive thrombosis despite therapy with anticoagulants.[15,29] The frequency of anticoagulant failures is not clear, but in the small study by Llitjos et al,[15] more than half of patients receiving therapeutic anticoagulation had progressive thrombosis. The evaluation and management of patients in whom anticoagulation therapy has clearly failed is complex and requires a multidisciplinary approach following 5 general principles. First, objectively confirm anticoagulant failure through careful side-by-side imaging review. Second, confirm proper medication dosing, absorption, and administration. An assessment of anticoagulation levels can be informative when feasible. For younger patients with preserved renal function, in particular, there may be increased metabolic clearance of LMWH, dabigatran, and edoxaban.[63,64] Drug interactions such as the concomitant use of strong CYP3A4 and P-glycoprotein inducers should be assessed. Attention to requirements of specific anticoagulants is needed; for example, adequate absorption

of rivaroxaban necessitates concomitant meals enriched in fat.[65] Additionally, drug absorption may be compromised by such conditions as disturbances in gastrointestinal motility, gastrointestinal resection, or gastric bypass.[66,67] Third, medication adherence in the outpatient setting is an important variable regardless of which anticoagulant is prescribed.[68-70] Fourth, temporary anticoagulant interruptions for invasive procedures may promote thrombosis for several reasons. Invasive procedures,[71-73] blood product transfusions, and central venous catheters all increase the thrombotic risk. Fifth, heparin-induced thrombocytopenia may complicate anticoagulation delivery for both unfractionated heparin or LMWH therapy. Lastly, there is growing evidence that the outcomes of antiphospholipid syndrome treatment are improved with warfarin compared with DOACs.[74,75] Whether this recommendation should be extended to COVID-19—associated antiphospholipid syndrome is not clear.

Once a careful multidisciplinary evaluation has been accomplished and clear anticoagulant failure has been confirmed, there are several untested management strategies one could pursue. These strategies address treatment of the underlying disease process and the cytokine-specific mechanisms, and changing anticoagulant therapy or method of delivery may be useful. For DOAC failures, changing to enoxaparin may improve efficacy. For enoxaparin failures, changing from once-daily (1.5 mg/kg per day) to twice-daily (1 mg/kg twice daily) administration may also be effective. For warfarin failures, switching to a DOAC or LMWH are options after careful assessment of the adequacy of the international normalized ratio (time in therapeutic range) has been reviewed and explored.

Limitations and Future Directions

Clear limitations of this work are the lack of evidence that warrants high certainty and the rapid process of developing this guidance. This guidance did not follow the typical process of clinical guideline development.[53] There are a number of unanswered questions relating to the coagulopathy and COVID-19.

(1) Most reported series are limited to ICU patients. Between 10% and 20% of patients infected with COVID-19 require hospitalization at a current overall rate of 29.2 per 100,000 individuals.[2] Of these patients, nearly 60% do not entail ICU admissions. There are currently limited data on VTE prevalence for patients hospitalized on the medical ward, apart from the ICU setting. Without these numbers, it is difficult to inform decision making for VTE prophylaxis of this sizeable patient population. Ideally, these rates would be compared with rates for hospitalized patients without COVID-19 receiving prophylaxis. Although randomized trials of different antithrombotic prophylaxis strategies are under way, data to inform decision making may not be available for some time.
(2) There are no estimates of VTE rates in ambulatory patients with COVID-19 recovering at home. Whether these patients should receive some form of DVT prophylaxis is unknown.
(3) A few reports exist regarding bleeding outcomes for these hospitalized patients receiving either prophylaxis or therapeutic anticoagulation.
(4) Ideal screening strategies for DVT or PE in the ICU setting are not known. Many of these patients may be mechanically ventilated in the prone position, making a thorough ultrasonographic examination challenging. The safety of sonographers obtaining these imaging studies must also be taken into account when designing screening strategies.
(5) Evaluation strategies relying on pretest probability of disease assessment may not be valid for patients with COVID-19, who seem to have a much higher rate of incident VTE compared with other populations.
(6) The use of D-dimer as a negative predictive assay to exclude patients without VTE may be of less value because the

laboratory hallmark of this disease appears to be an elevated D-dimer value.

Future studies should therefore determine more precise incident data on all patients with COVID-19 infections to better inform VTE prophylaxis recommendations. When feasible, defining the timing of greatest risk from the onset of infection to the time of VTE would help guide both the timing and the intensity of anticoagulant delivery. Risk assessment tools and validated evaluation strategies unique to COVID-19 would also be helpful. Defining the optimal use of screening imaging including both computed tomographic angiography and ultrasonography would help direct resource utilization in this disease. When possible, institutions should consider activation and patients should be enrolled into clinical trials. As of May 30, 2020, there are 2 trials listed on the ClinicalTrials.gov website (NCT04367831 and NCT04359277).

Lastly, the precise mechanism driving the COVID-19 coagulopathy requires further study. There are several intriguing hypotheses including complement-mediated thrombogenesis. In this model, membrane attack complex–mediated endothelial injury with subsequent coagulation activation has been postulated as the driving mechanism for small vessel thrombosis, end-organ damage, and associated fibrin D-dimer production.[76,77] A second hypothesis focuses on the central role of neutrophil activation with neutrophil extracellular traps formation resulting in widespread organ injury.[78-80] Severe COVID-19 infection has been associated with a "cytokine storm," including interleukin, interferon-γ, tumor necrosis factor, and granulocyte colony-stimulating factor release leading to an uncontrolled positive signaling loop between macrophages and neutrophils. In this model, endothelial infection with SARS-COV-2 leads to endothelial activation promoting neutrophil recruitment. Activated neutrophils then release neutrophil extracellular traps, large extracellular weblike structures containing cytosolic and granular proteins within a scaffold of decondensed nuclear chromatin. NETosis is a highly regulated process that serves as a robust mechanism for thrombus initiation by promoting platelet aggregation and coagulation activation. A third mechanism suggests that the coagulopathy is primarily driven by hypoxia.[81-84] Severe COVID-19 infections result in bilateral pneumonia, thick secretions, extensive lung parenchyma damage, hypoxia, and acute respiratory distress syndrome. Hypoxic conditions are known to stimulate platelet and neutrophil adhesion to endothelial cells, tissue factor expression while suppressing tissue factor pathway inhibitor and fibrinolytic pathways. It is likely that the pathophysiology of SARS-CoV-2–related coagulopathy cannot be easily parsed into systems and that each mechanism described here plays a role, perhaps in tandem or in sequence.

CONCLUSION

SARS-CoV-2 causing COVID-19 has infected a large number of individuals in our country and worldwide. Infection with this virus has a unique laboratory signature including thrombocytopenia with elevated fibrinogen and fibrin D-dimer, all of which are associated with poor outcomes. Thrombotic outcomes add to the morbidity and mortality and require a thoughtful approach to VTE prophylaxis, balancing the risk of thrombosis with the risk of major bleeding. We present guidance on prevention and management of thrombosis based on low-certainty evidence. We await future studies that enable the formal development of rigorous clinical practice guidelines.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviationsand Acronyms: **aPTT** = activated thromboplastin time; **COVID-19** = coronavirus disease 2019; **DIC** = disseminated intravascular coagulation; **DOAC** = direct oral anticoagulant; **DVT** = deep venous thrombosis; **ICU** = intensive care unit; **LMWH** = low-molecular-weight heparin; **OR** = odds ratio; **PE** = pulmonary embolism; **PT** = prothrombin time; **SARS-CoV** = severe acute respiratory syndrome coronavirus; **SC** = subcutaneously; **VTE** = venous thromboembolism

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