Thrombosis in COVID-19: A Narrative Review of Current Literature and Inpatient Management

ANDREW HSU, MD; SARAH OHNIGIAN, MD; AUGUSTUS CHANG, MD; YUCHEN LIU, MD; ADAM S. ZAYAC, MD; ADAM J. OLSZEWSKI, MD; JOHN L. REAGAN, MD

ABSTRACT

COVID-19 infection has been associated with an increased incidence of thrombotic events leading to poor patient outcomes. Given the rapid rise of the COVID-19 pandemic, the ability to conduct prospective trials has been limited and data regarding the use of standard-dose versus intermediate-dose thromboprophylaxis, use of empiric therapeutic anticoagulation, and use of extended-duration thromboprophylaxis after discharge has been largely based upon observational data without any high-quality prospective data guiding their use. In this article, we will review the incidence and frequency of arterial and venous thrombotic events along with the current literature surrounding the use of intermediate-dose thromboprophylaxis, empiric therapeutic anticoagulation, and use of extended-duration thromboprophylaxis for patients hospitalized with COVID-19.

KEYWORDS: coronavirus 2019, COVID-19, COVID-19 coagulopathy, thrombosis, anticoagulation

INTRODUCTION

In December 2019, a novel coronavirus pneumonia of unknown origin emerged in Wuhan, China. The pathogen that was subsequently implicated, Coronavirus 2019 (COVID-19), was a novel enveloped RNA betacoronavirus which behaved similarly to the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.[1,2]

Early publications described a variety of symptoms along with abnormal coagulation parameters – prolonged prothrombin time and partial thromboplastin time, elevated D-dimer and fibrinogen levels, and decreased antithrombin activity.[3-5] A retrospective study observed that derangements in coagulation parameters were associated with poorer patient outcomes – patients whose abnormal coagulation parameters met the International Society of Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulopathy (DIC) demonstrated decreased survival.[6]

Furthermore, early literature described an underlying inflammatory state in COVID-19. This initial investigation was spurred by the high pathogenicity previously seen in SARS-CoV and MERS-CoV where studies demonstrated an increased amount of proinflammatory cytokines.[7,8] Similarly, patients with COVID-19 displayed increased proinflammatory markers suggesting that an underlying inflammatory state played a critical role in the development of acute respiratory distress syndrome (ARDS) seen in these viral infections.[3-5] Post-mortem examination of COVID-19 patients demonstrated direct viral infection of the endothelial cells leading to diffuse endothelialitis, microvascular dysfunction, and widespread thrombotic microangiopathy, supporting previous observations regarding the higher incidence of DIC in COVID-19 non-survivors.[6, 9,10]

Given these findings, it has been thought that altered coagulation parameters in COVID-19 are a marker of thrombotic complications rather than bleeding risk. Tang et al demonstrated improvement in 28-day mortality in severe COVID-19 patients with markedly elevated D-dimer levels who received thromboprophylaxis with either low-molecular-weight heparin (LMWH) at 40-60mg daily or subcutaneous unfractionated heparin (UFH) at 10,000–15,000 IU daily.[11] This finding led to the adoption of prophylactic anticoagulation in the management of hospitalized COVID-19 patients.[12-15] This practice has varied from institution to institution and included: D-dimer guidance for the initial choice of anticoagulation; use of higher intensity or therapeutic anticoagulation; and extended-duration prophylaxis.[16-18] The aim of this review is to the summarize the literature surrounding the frequency and incidence of thrombotic events along with the literature surrounding the management and prevention of thrombosis in hospitalized COVID-19 patients.

VENOUS THROMBOEMBOLISM (VTE)

Early in the pandemic, there was an observed increased incidence of thrombotic events in hospitalized COVID-19 patients and it was recognized that VTE [pulmonary embolism (PE) and deep venous thrombosis (DVT)] were common complications.[19,20] The incidence of VTE in these reports were variable and subject to selection bias with overrepresentation of critically-ill patients, differences in study design, geographical differences, and other variables.[11,19,20]

Given these variations, Nopp et al performed a meta-analysis to determine the prevalence of VTE after excluding

studies determined to have a high risk of bias. Ultimately, 66 retrospective studies were determined to have low risk of bias and involved 28,173 total patients (1,819 ambulatory patients, 20,886 non-ICU patients, 5,468 ICU patients) who developed 1,824 total VTEs, which consisted of DVTs (including catheter-related thrombosis), PEs, or VTEs (composite of both), as defined within the retrospective studies. The pooled prevalence of VTEs was 14.1% (95% confidence interval [CI], 11.6–16.9; I^2, 97.1%). In the ICU, the pooled prevalence of VTEs was 22.7%, PE was 13.7% and DVT was 18.7%. In non-ICU patients, the pooled prevalence of VTEs was 7.9%, PE was 3.5%, and DVT was 4.1%.[20] In contrast, a prior study examining the incidence of DVT/PE in hospitalized patients by evaluating the National Hospital Discharge Survey found a DVT incidence of 1.3% and PE incidence of 0.4%.[21] In the medical ICU setting, studies regarding the incidence of DVT and PE with thromboprophylaxis ranges between 5–23% and 0.7–6%, respectively.[22-24] Therefore, when compared to historical data COVID-19 appears to be associated with a higher incidence of VTE in the ICU, non-ICU, and aggregate setting.

Helms et al compared 150 ICU patients with COVID-19 ARDS to a historical cohort of 233 ICU patient with non-COVID-19 ARDS. After matching, there were more VTEs in the COVID-19 cohort (11.7% vs 4.8%; p=0.035) along with significantly more PEs (11.7% vs 2.1%; p=0.008). Both cohorts were either on prophylactic or therapeutic anticoagulation.[25] In another study examining the incidence of PE, 107 ICU patients with COVID-19 were compared to a historical cohort of 40 ICU patients with H1N1 influenza, and a historical cohort of 196 ICU patients admitted for neither influenza nor COVID-19. The cumulative incidence of PE was 20.6% vs 7.5%, respectively (absolute risk [AR] 13.1%; 95% CI, 1.9-24.3) vs 6.1% (AR 14.4%; 95% CI, 6.1–22.8).[26] Both studies demonstrate an observed higher incidence of thrombotic events when compared to non-COVID-19 patients or other viral pneumonias.

ARTERIAL THROMBOEMBOLISM (ATE)

Early literature described an increased incidence of VTE; however, as the pandemic progressed there was growing literature regarding an increased incidence of ATEs – strokes (CVA), myocardial infarctions (MI), systemic arterial embolism, and acute limb ischemia (ALI).[27,28] Bilaloglu et al studied 3,334 hospitalized COVID-19 patients, of whom 365 developed ATEs (1.6% CVA, 8.9% MI, 1% systemic thromboembolism). In 829 ICU patients, 18.6% experienced an ATE. In 2,505 non-ICU patients, 8.4% experienced an ATE.[27] A meta-analysis found that 8 of the 42 studies in the analysis reported ATEs with an overall incidence of 2%; however, in the non-ICU setting the incidence was 1% compared to 5% in the ICU setting. The pooled incidences per specific ATEs were: MI 0.5%, CVA 1%, and ALI 0.4%.[28]

MONITORING COAGULATION PARAMETERS

Many institutions have adopted the practice of checking coagulation parameters not only on admission but also throughout hospitalization as it is thought to provide prognostic value.[3,4,6] In early observational data, elevated D-dimer levels on admission or levels that increased during hospitalization were associated with higher in-hospital mortality.[6,12] COVID-19 non-survivors had larger increases in D-dimer and fibrinogen levels when compared to COVID-19 survivors.[6,28] Based upon these observations, many institutions implemented aggressive diagnostic and therapeutic interventions even in the absence of clinical signs of VTE. However, it is unclear whether these elevated D-dimer levels are a marker of severe inflammation and the resultant cytokine storm in patients with severe disease rather than a reliable predictor of VTE. Given the uncertainty, societies such as the American Society of Hematology (ASH), CHEST, and ISTH do not incorporate the use of conventional coagulation parameters to guide anticoagulation (**Table 1**); however, many ongoing prospective trials are incorporating D-dimer levels to help stratify patients which may provide information regarding its utility.[13-15]

VTE PROPHYLAXIS

Early in the pandemic, the use of pharmacological VTE prophylaxis was adopted based upon the findings that its use was associated with an improved 28-day mortality (p=0.03). It was also noted that in patients who did not receive heparin-products (LMWH, UFH), mortality rose with rising D-dimer levels > 6 times the upper limit of normal (p=0.02).[11] However, questions remained regarding the adequacy of standard-dose thromboprophylaxis (defined as LMWH 40mg daily or subcutaneous UFH 5000 IU three times daily) in this population, particularly in critically-ill COVID-19 patient, which has led to the widespread use of dose-escalated prophylaxis and therapeutic anticoagulation.

INTERMEDIATE-DOSE PROPHYLAXIS

Given the paucity of data surrounding the use of intermediate-dose prophylaxis prior to the COVID-19 pandemic, Eck et al conducted a meta-analysis of 70 randomized trials examining intermediate-dose LMWH prophylaxis versus placebo. Ultimately, it was found that use of intermediate-dose LMWH prophylaxis led to a minimal, but statistically significant improvement in all-cause mortality at the cost of a statistically significant increase in major bleeding (defined as fatal bleeding; symptomatic bleeding in critical area/organ including intracranial bleed; or bleeding leading to transfusion of $\geq$ 2 units of red cells).[29] However, given an increased incidence of thrombosis associated with a higher mortality in COVID-19 patients, many institutions empirically incorporated the use of intermediate-dosing prophylaxis with variable outcomes.[17]

Table 1. Summary of Societal Recommendations for Thromboprophylaxis in COVID-19[13-15]

	American Society of Hematology (ASH)	International Society for Thrombosis and Haemostasis (ISTH)	CHEST
Lab† Guidance in Anticoagulation Choice or Escalation	NR	NR	NR
Thromboprophylaxis (includes intermediate-dose and therapeutic anticoagulation)	Prophylactic-intensity over intermediate- or therapeutic-intensity anticoagulation in acutely-ill and/or critically-ill COVID-19 patients without suspected or confirmed VTE.	Prophylactic–dose UFH or LMWH in acutely-ill and/or critically-ill COVID-19 patients after assessing bleeding risk. Intermediate-dose LMWH can be considered in high-risk patients. Obese patients defined by actual body weight or BMI should consider a 50% increase in the dose of thromboprophylaxis. Would not consider treatment-dose as prophylaxis.	Prophylactic-dose anticoagulation in acutely-ill and/or critically-ill COVID-19 patients over intermediate or full treatment dosing.
Extended-Duration Thromboprophylaxis	NR	Should be considered patients that meet high-risk criteria. Recommend use of LMWH or DOAC. Duration can be 14-30 days.	Do not routinely recommend, but can consider in patients at low risk of bleeding and increased VTE risk.

† Labs include prothrombin time, partial thromboplastin time, D-dimer, fibrinogen; NR: no recommendation; RCT: randomized controlled trial; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; "critically-ill" defined as patients suffering from a life-threatening condition who would typically be admitted to an intensive care unit (ICU)

Rannuci et al performed a prospective observational study of 16 ICU patients with COVID-19 ARDS to characterize their coagulation profile through standard coagulation parameters and viscoelastic coagulation tests. In this study, lab parameters were monitored after increases to intermediate-dose LMWH. After 7 days of the increase to intermediate-dose LMWH there were significant time-related decreases in fibrinogen levels (p=0.001), D-dimer (p=0.02) and improved viscoelastic testing suggesting a decrease in hypercoagulability and clot firmness.[30] Similarly, in a retrospective study of 468 patients, those with severe COVID-19 who received intermediate-dose prophylaxis (defined as LMWH 40mg twice daily or subcutaneous UFH 7500 IU three times daily) were shown to have stable or decreasing D-dimer levels while patients who only received standard-dose prophylaxis were observed to have D-dimer levels significantly increase during their hospitalizations (p<0.001). It was also found that the use of intermediate-dose prophylaxis was associated with improved 30-day mortality (p=0.045) without significant differences in bleeding (p=0.1).[17]

INSPIRATION was a randomized trial examining the use of intermediate-dose LMWH (defined as 1mg/kg daily) versus standard-dose prophylaxis in 660 patients with COVID-19 in the ICU. The use of intermediate-dose was not associated with significant differences in 30-day mortality (43.1% vs 40.9%; p=0.50), risk of VTE (3.3% vs 3.5%; p=0.94), ATE in the form of CVAs (0.3% vs 0.4%; p=0.97), ventilator-free days (30 vs 30 days; p=0.50), or ICU length of stay (5 vs 6 days; p=0.14). There was a numerically higher rate of major bleeding (2.5% vs 1.4%) with use of intermediate-dose prophylaxis but did not meet the pre-defined noninferiority criteria; however, there was no significant difference in rate of non-major bleeds (4.3% vs 1.5%; p=0.07).[31]

In the ICU setting, this prospective randomized trial has demonstrated no differences in outcomes with numerically increased major bleeding events. However, the role of intermediate-dose prophylaxis in the non-ICU setting remains unclear and ongoing prospective trials are underway to answer this question.

THERAPEUTIC ANTICOAGULATION

Another strategy in dose-escalated anticoagulation has been the empiric use of treatment-dose or therapeutic anticoagulation. Paranjpe et al conducted one of the earliest retrospective studies examining the use of therapeutic anticoagulation. In 395 mechanically ventilated patients who received therapeutic anticoagulation, there was improved 21-day mortality (29.1% vs 62.7%) but not in other subsets (22.5% vs 22.8%). It was observed that a longer duration of therapeutic anticoagulation was associated with reduced mortality (p<0.001). Of note, there was no increased rate of bleeding events among those that received therapeutic anticoagulation (1.9% vs 3%; p=0.2).[16]

In a follow-up trial that retrospectively included 4,389 patients showed that use of therapeutic anticoagulation was associated with a 47% reduction in mortality (p<0.001) when compared with no anticoagulation. However, the use of standard prophylaxis was associated with a 50% reduction in mortality (p<0.001) compared with no anticoagulation. In adjusted analysis comparing therapeutic anticoagulation to prophylaxis, there was a non-statistically

significant reduction in mortality (p=0.08). Furthermore, the use of therapeutic anticoagulation was associated with a 31% reduction in the incidence of intubation (p=0.02) compared to no anticoagulation. Similarly, prophylaxis was associated with a 28% reduction in the incidence of intubation (p=0.003) compared with no anticoagulation. Adjusted analysis showed no statistical difference in incidence of intubation between the two interventions (p=0.63). Overall major bleeding rates, counted only after initiation of anticoagulation treatment, were low (2%); however, the rate was proportionally highest in patients who received therapeutic anticoagulation (3.0%), followed by no anticoagulation (1.9%) and lowest in standard prophylaxis (1.7%).[32]

HESACOVID, the only published prospective study examining empiric use of therapeutic anticoagulation in COVID-19, was an open-label, phase II randomized trial comparing the use of therapeutic enoxaparin (defined as 1mg/kg twice daily) versus standard prophylaxis (defined as subcutaneous UFH 5000 IU three times daily or enoxaparin 40 mg daily). This trial enrolled 20 total patients who were mechanically ventilated. Therapeutic enoxaparin led to a higher ratio of successful 28-day liberation from mechanical ventilation (p=0.031) and a decrease in D-dimer levels (4176 µg/L vs 1469 µg/L; p=0.009). In the standard prophylaxis group, D-dimer levels demonstrated an increase over time (3408 µg/L vs 4878 µg/L; p=0.004). There was no difference in all-cause 28-day mortality between therapeutic enoxaparin versus standard prophylaxis (p=0.26), in-hospital mortality (p=0.16), or ICU-free days (p=0.07). Although this study did not actively investigate thrombotic events each group had 2 VTEs (2 DVT in the therapeutic group; 1 DVT and 1 PE in the prophylactic group). There were no major bleeding events.[33] These results, coupled with the decreasing D-dimer levels, is suggestive of anti-inflammatory properties of higher doses of anticoagulation, similar to the previous findings of Rannuci et al.[30]

Current societal guidelines regarding the use of therapeutic anticoagulation state that in the absence of a clear indication for therapeutic anticoagulation (i.e., newly-confirmed, recent history, or suspected VTE, atrial fibrillation, mechanical cardiac valves, or long-term secondary VTE prevention) the use of empiric therapeutic anticoagulation is not recommended for ICU or non-ICU patients.[13-15] Several randomized trials are underway to examining the empiric use of therapeutic anticoagulation in COVID-19. Of note, the interim analysis of three randomized trials (ACTIV-4a, REMAP-CAP, ATTACC) led to a pause in enrollment in critically-ill patients admitted to the ICU over concerns of futility for efficacy (e.g., no reduction in need for organ support) and increased safety events (e.g., major bleeding). The publication with additional clarifications is pending; however, current societal guidelines recommend the use of standard-dose thromboprophylaxis.[13-15,34]

EXTENDED-DURATION PROPHYLAXIS

Given the higher incidence of thrombosis in patients hospitalized with COVID-19, there has been concern for the development of thrombotic events after discharge, prompting some institutions to prescribed extended-duration VTE prophylaxis. Prior to the pandemic, the practice of extended-duration VTE prophylaxis for non-surgical patients was largely based upon multiple outcome studies that demonstrated that a large proportion of hospital-associated VTEs occurred post-discharge, and most within 6 weeks after discharge.[35,36] This has prompted the development of the modified IMPROVE score based upon several clinical factors (**Table 2**) where groups deemed high-risk derived benefit from VTE prophylaxis after discharge.[37,38]

Since the start of the pandemic, a retrospective study examined 1,877 patients discharged after hospitalization with COVID-19 observed 9 hospital-associated VTEs. This was compared to a historical cohort of 18,159 medical patients who were discharged and found to have 56 hospital-associated VTEs. This study demonstrated that COVID-19 hospitalization did not appear to have an increased risk of post-discharge VTE.[39] Another retrospective study examined 163 patients after hospitalization with COVID-19 and observed 4 thrombotic events. The cumulative 30-day incidence of overall thrombosis after discharge was 2.5% and the cumulative 30-day incidence of VTEs after discharge was 0.6%.[40] When these results are compared to the control arms of prior randomized trials examining the use of extended-duration VTE prophylaxis in medical patients, COVID-19 does not appear to be associated with an increased incidence of VTE after hospitalization.[35,36]

Multiple societies do not provide any recommendation regarding the use of extended-duration VTE prophylaxis.[13-15] However, ISTH states that extended-duration VTE prophylaxis should be considered for patients meeting high-risk criteria based upon the modified IMPROVE score.[13]

Table 2. Modified IMPROVE Score[38]

Risk Factor	VTE Risk Score
Prior VTE	3
Diagnosed thrombophilia*	2
Current lower limb paralysis or paresis**	2
History of cancer†	2
D-dimer > 2 times upper limit of normal	2
ICU or coronary care unit stay	1
Complete immobilization‡ > 1 day	1
Age > 60 years	1

High Risk Score > 4 corresponding with a nearly three-fold higher VTE risk at discharge and warrants consideration for extended-duration VTE prophylaxis; *Congenital or acquired condition leading to increased risk of thrombosis; **Leg falls to bed by 5 seconds but has some effort against gravity (taken from National Institute of Health Stroke Scale); †Cancer present at any time in past 5 years; ‡Defined as confined to bed or chair with or without bathroom privileges.

CONCLUSION

The COVID-19 pandemic has gripped the medical community, disrupting routines and normal hospital workflow, and its management has changed at a seemingly dizzying pace. Based upon early observational data, COVID-19 patients develop an inflammatory response leading to an increased incidence of thrombosis.[6,9-11] The practice of intermediate-dose prophylaxis, empiric therapeutic anticoagulation, and extended-duration prophylaxis has been largely guided by observational studies. Of the published prospective trials, INSPIRATION has demonstrated no differences in outcomes with intermediate-dose prophylaxis in the ICU population, and HESACOVID has demonstrated a higher ratio of successful liberation from mechanical ventilation with therapeutic anticoagulation. Current guidelines recommend managing hospitalized COVID-19 patients similarly to any acutely ill patient – routine use of pharmacological VTE prophylaxis, unless medically contraindicated, with some societies considering intermediate-dose prophylaxis.[13-15] Therapeutic anticoagulation is reserved for patients with other clear indications for anticoagulation.[13-15] Similarly, extended-duration prophylaxis is reserved for patients deemed to be at high-risk based upon the modified IMPROVE score.[13,38] There are several ongoing, prospective trials hoping to provide high-quality evidence to help guide VTE prevention and management in COVID-19.

References

1. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019 Mar;17(3):181-192.
2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720.
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513.
6. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844-847.
7. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004 Apr;136(1):95-103.
8. Mahallawi WH, Khabour OF, Zhang Q, et al. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine. 2018 Apr;104:8-13.
9. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020 May 2;395(10234):1417-1418.
10. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120-128.
11. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-1099.
12. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Jun;18(6):1324-1329.
13. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1859-1865.
14. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. Chest. 2020 Sep;158(3):1143-1163.
15. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021 Feb 9;5(3):872-888.
16. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020 Jul 7;76(1):122-124.
17. Hsu A, Liu Y, Zayac AS, et al. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. Thromb Res. 2020 Dec;196:375-378.
18. Daughety MM, Morgan A, Frost E, et al. COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy. Thromb Res. 2020 Dec;196:483-485.
19. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1995-2002.
20. Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost. 2020 Sep 25;4(7):1178-1191.
21. Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. Am J Cardiol. 2005 Jun 15;95(12):1525-1526.
22. Bahloul M, Chaari A, Kallel H, et al. Pulmonary embolism in intensive care unit: Predictive factors, clinical manifestations and outcome. Ann Thorac Med. 2010 Apr;5(2):97-103.
23. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med. 2005 Jul;33(7):1565-1571.
24. Ibrahim EH, Iregui M, Prentice D, et al. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. Crit Care Med. 2002 Apr;30(4):771-774.
25. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098.
26. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation. 2020 Jul 14;142(2):184-186.
27. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020 Aug 25;324(8):799-801.
28. Malas MB, Naazie IN, Elsayed N, et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 2020 Dec;29:100639.
29. Eck RJ, Bult W, Wetterslev J, et al. Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Semin Thromb Hemost. 2019 Nov;45(8):810-824.

30. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020 Jul;18(7):1747-1751.
31. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021 Mar 18;e214152.
32. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020 Oct 20;76(16):1815-1826.
33. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res. 2020 Dec;196:359-366.
34. NIH ACTIV trial of blood thinners pauses enrollment of critically ill COVID-19 patients. News release. National Institutes of Health. December 22, 2020. Accessed March 20, 2021. https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients
35. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med. 2010 Jul 6;153(1):8-18.
36. Mahan CE, Fisher MD, Mills RM, et al. Thromboprophylaxis patterns, risk factors, and outcomes of care in the medically ill patient population. Thromb Res. 2013 Nov;132(5):520-526.
37. Spyropoulos AC, Anderson FA Jr, FitzGerald D, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest. 2011 Sep;140(3):706-714.
38. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE Risk Score and Elevated D-Dimer Identify a High Venous Thromboembolism Risk in Acutely Ill Medical Population for Extended Thromboprophylaxis. TH Open. 2020 Mar 13;4(1):e59-e65.
39. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood. 2020 Sep 10;136(11):1347-1350.
40. Patell R, Bogue T, Koshy A, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood. 2020 Sep 10;136(11):1342-1346.

Authors

Andrew Hsu, MD, Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Providence, RI.

Sarah Ohnigian, MD, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Augustus Chang, MD, Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Yuchen Liu, MD, Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Adam S. Zayac, MD, Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Providence, RI.

Adam J. Olszewski, MD, Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Providence, RI.

John L. Reagan, MD, Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

Conflicts of Interest: The authors declare no conflicts of interest.

Correspondence

Andrew Hsu, MD
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
401-444-2330
Andrew_hsu1@brown.edu