Hypercoagulability and coronavirus disease 2019–associated hypoxemic respiratory failure: Mechanisms and emerging management paradigms

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the viral respiratory illness coronavirus disease 2019 (COVID-19). Up to 20% of these patients require hospital and critical care resources because of hypoxemic respiratory failure, which has overwhelmed healthcare systems.[1,2] Coronavirus disease 2019 patients with severe acute lung injury (ALI) present in a characteristic manner with 5 to 10 days of febrile illness and viral respiratory tract symptoms and bilateral infiltrates on chest radiography, followed by progressive hypoxemia with or without respiratory distress.[3,4] About 3% to 5% of patients develop a rapidly evolving acute respiratory distress syndrome (ARDS), like decompensation.[2,4,5]

Coronavirus disease 2019 patients are prone to coagulopathy, a broad term that defines any derangement of hemostasis resulting in either excessive bleeding or clotting.[6] In contrast to patients with severe sepsis from other causes, disseminated intravascular coagulation (DIC), a consumptive coagulopathy often associated with bleeding, is uncommon with COVID-19. Instead, most patients with COVID-19 have a hypercoagulable state with elevated levels of fibrinogen, factor VIII, and von Willebrand factor (vWF). These findings, together with high levels of D-dimer levels, manifest clinically as thromboembolic complications including deep vein thrombosis (DVT), pulmonary embolism (PE), and ischemic stroke.[7] The development of ALI and associated hypoxemic respiratory failure in COVID-19 appear to be due to pulmonary microvascular thrombosis and intra-alveolar fibrin deposits.[8–10] The thromboinflammatory response and microvascular thrombosis may provide important therapeutic targets to mitigate ALI.[11] However, the specific coagulation and fibrinolysis defects in COVID-19–associated coagulopathy (CAC) are incompletely understood, and it remains unclear why some patients progress toward ARDS. This article focuses on (1) the mechanisms by which CAC develops, (2) potential pathways through which CAC may contribute to progressive lung injury, and (3) considerations for management of CAC depending on disease severity and the extent of the coagulopathy.

BURDEN OF COAGULOPATHY IN COVID-19

Coronavirus disease 2019 causes a prothrombotic state with macrovascular complications (stroke, DVT/PE), and microvascular thrombosis, potentially driving ALI and multiorgan failure. Bleeding is a rare complication. Venous thromboembolism was found in 25% of a cohort of 81 COVID-19 patients admitted to the intensive care unit (ICU) in Wuhan where routine thromboprophylaxis is rarely provided.[12] Despite thromboprophylaxis, a study from The Netherlands that included 184 patients with COVID-19 admitted to the ICU reported a 31% incidence of PE, DVT, ischemic stroke, or myocardial infarction.[13] In a prospective cohort study from France, thromboembolic events (including PE and dialysis circuit clotting), occurred in 64 (43%) of 150 patients with COVID-19 admitted to the ICU despite routine anticoagulant thromboprophylaxis.[14]

The inflammatory and coagulopathic response in COVID-19 may be a central driver of lung injury. In a retrospective single-center study of 1,008 patients with COVID-19 pneumonia in Wuhan, the diagnosis of PE was confirmed in 10 (40%) of 25 patients who underwent computed tomography pulmonary angiography for suspected PE.[15] Although all of the patients had elevated levels of D-dimer, the mean D-dimer level was significantly higher in those with confirmed PE than in those without PE. In most cases, PE was multilobar and involved small distal segmental or subsegmental arteries. Initial histopathologic studies reveal thrombosis in the lung microvasculature with areas of diffuse alveolar damage containing intra-alveolar fibrin deposits with entrapped neutrophils possibly representing neutrophil extracellular traps (NETs).[8–10,16] Autopsy results have shown that a proportion of such patients have unsuspected DVT.[10] Thus, microvascular thrombosis from CAC may accelerate ALI and hypoxemic respiratory failure.

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MECHANISM OF COVID-19–ASSOCIATED COAGULOPATHY

The SARS-CoV-2 virus directly enters alveolar epithelial cells via the angiotensin-converting enzyme 2 receptor (Fig. 1).[17] Infected epithelial cells generate a dysregulated inflammatory response cytokine storm,[18] potentially causing hypercoagulability via activation of multiple procoagulant pathways and disruption of anticoagulant systems. It is well established that sepsis and, in particular, pneumonia-induced ALI[19] begin as an inflammation-driven prothrombotic state (immunothrombosis),[20] which drives multiorgan failure, ending with DIC in some patients.[21] This acute phase is characterized by five primary insults (reviewed in detail by Iba et al.[21]).

1. Coagulation activation is initiated by inflammatory responses caused by recognition of pathogen-associated molecular patterns by pattern-recognizing receptors.[22] These induce the widespread release of proinflammatory cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor α), thus increasing the expression of tissue factor and inducing NETosis, which are processes that lead to coagulation activation through the extrinsic and intrinsic pathways, respectively.[23,24]
2. Endothelial cells also express angiotensin-converting enzyme 2 receptors, and viral infection of the vascular endothelium may cause upregulation of tissue factor and vWF expression, destruction of the endothelial glycocalyx, and release of tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1). The resultant disruption of the antithrombotic phenotype of the endothelium may be a major driver of CAC.
3. Platelets are activated by infectious agents, proinflammatory cytokines, thrombin, and increased vWF expression.[7,25,26]
4. Endogenous anticoagulant systems become dysregulated via mechanisms that include loss of endothelial glycocalyx with reduced heparan sulfate catalysis of antithrombin and reduced protein C activation because of shedding of thrombomodulin and endothelial protein C receptor.[27]
5. Fibrinolytic suppression occurs later in the course of infection because of increased PAI-1 release. Thus, early fibrinolysis driven by tPA released from damaged tissues causes the elevation in D-dimer levels. Rebound suppression occurs later via PAI-1 and is a harbinger to the end organ dysfunction observed in sepsis-induced DIC.[28]

High levels of proinflammatory cytokines such as IL-2, IL-7, granulocyte-macrophage colony-stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1A, and tumor necrosis factor α are found in COVID-19 patients.[1] Severe disease is characterized by a cytokine storm with uncontrolled innate inflammatory and adaptive immune responses.[29] Biomarkers of exhaustion are increased (NKG2A), and lymphopenia is common with decreased numbers of CD4+, as well as CD8+ T cells, B cells, and natural killer cells.[29] Acute phase biomarkers are increased, demonstrated by an increase in fibrinogen, C-reactive protein, ferritin, lactate dehydrogenase, IL-6, vWF, and factor VIII.[3,30] The inflammatory response associated with the cytokine storm triggers a procoagulant state[11] with abnormal coagulation tests including prolongation of the prothrombin time and, less frequently, the activated partial thromboplastin time.[6,31–33] However, D-dimer has emerged as the biomarker most closely correlated with disease severity, progression, and mortality.[34]

COVID-19–ASSOCIATED COAGULOPATHY AND ALI

The overwhelming pathology in COVID-19 is hypoxemic respiratory failure from an ARDS-like process. In ARDS, inflammatory airspace disease leads to diffuse destruction of alveoli, increased capillary permeability, and development of alveolar edema.[35] This results in decreased lung compliance and pulmonary shunting, causing hypoxemia, ventilatory failure, and right heart failure. The mainstay of treatment is supportive ventilation with low tidal volumes and pulmonary pressures.[35]

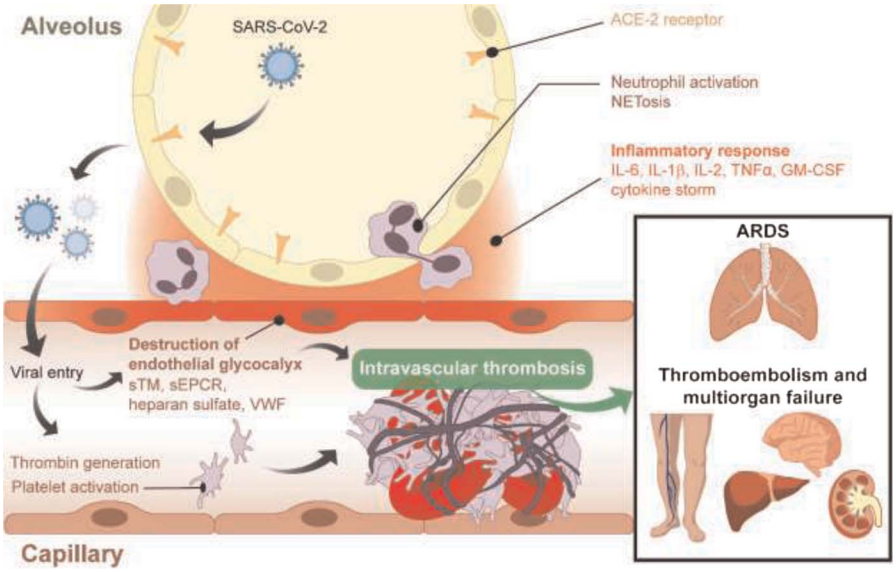

Figure 1. The SARS-CoV-2 viral infection–driven immunothrombosis.

In early COVID-19 pneumonia, the traditional ARDS criteria may not be fully applicable.[36,37] Most patients with COVID-19 pneumonia have normal respiratory compliance. Some reports suggest that early traditional ARDS-type ventilator support may worsen ALI in COVID-19.[36] In contrast to the pathology of typical ARDS, histopathology suggests that alveolar capillaries have primarily microvascular thrombosis, with colocalized neutrophils and fibrin deposits, possibly including NETosis.[8,11,24] A subset of patients with severe COVID-19–related lung injury shows few signs of fibroproliferative changes characteristic of classic ARDS.[38]

An Italian intensive care group suggested that COVID-19 pneumonia and ALI predominantly present as "Type L," compliant lungs with hypoxemia explained by decreased perfusion from hypoxic vasoconstriction.[36] As ALI proceeds, there is a transition to "Type H" fitting the traditional features of ARDS—noncompliant lungs with fibroproliferative changes.[35] The progression from ALI to traditional ARDS may be driven by the inflammatory coagulopathy. Like the changes reported in severe influenza pneumonia-driven ARDS, the inflammatory storm with subsequent triggering of systemic thrombosis, fibrinolysis resistance, and loss of anticoagulant mechanisms may be a hallmark of COVID-19.[19] Therefore, early identification and management of coagulopathy may prevent the progression of hypoxemic respiratory disease in COVID-19.

EMERGING MANAGEMENT PARADIGMS AND CONSIDERATIONS FOR EMERGENCY DEPARTMENT AND ACUTE CARE MANAGEMENT

The Role of Anticoagulation

If thromboinflammation is the driving factor for the development of ARDS, early anticoagulant administration may reduce disease progression and save lives. In critically ill COVID-19 patients, the incidence of thromboembolic disease may be as high as 40% despite routine thromboprophylaxis, suggesting the need to evaluate therapeutic anticoagulation in this population.[14] The most robust predictor of death has been an elevated D-dimer level. In an early retrospective cohort of 191 patients from two Wuhan hospitals, D-dimer levels more than 1,000 μg/L (approximately two times the upper limit of normal in most laboratories) were associated with an odds ratio of 18 for mortality.[3] The D-dimer level begins to increase more than 1,000 μg/L 5 to 10 days into the course of the disease, possibly coinciding with the development of hypoxemic respiratory failure.[3] In critically ill patients where D-dimer levels were greater than 3,000 μg/L, prophylactic anticoagulation was associated with a 20% reduction in mortality.[39] Furthermore, in a retrospective cohort of 2,773 patients in a single center, the use of full dose systemic anticoagulation reduced mortality in patients requiring mechanical ventilation.[40]

Guidance from the International Society on Thrombosis and Hemostasis (ISTH) suggests early risk stratification for admission and thromboprophylaxis for patients with COVID-19 including determination of D-dimer and fibrinogen levels as well as the prothrombin time and platelet count.[41] The American Society of Hematology,[42] American College of Cardiology,[43] and, more recently, the ISTH Scientific and Standardization Committee on Perioperative, Critical Care on Thrombosis and Haemostasis[44] have also published anticoagulation guidance documents. Although there is no single or group of parameters that can guide the need for hospital admission or anticoagulation, COVID-19 patients are now known to be at high risk for thromboembolism. The ISTH DIC scores are low in COVID-19 patients. However, the sepsis-induced coagulopathy (SIC) score may be helpful to identify patients at risk for progression to DIC[21] and could be used to identify those requiring high-intensity care and those who might be candidates for intensified anticoagulant thromboprophylaxis.

Because of the high baseline prevalence of venous thromboembolism in COVID-19 patients admitted to hospital, recent interim guidance documents have suggested venous thromboembolism (VTE) risk assessment for all patients with COVID-19 admitted to the hospital and administration of prophylactic doses of heparin or low molecular weight heparin to those without contraindications.[43] Initiation of thromboprophylaxis could be expedited by incorporating thromboprophylaxis into emergency department order sets for COVID-19 patients referred for hospital admission. In critically ill patients, consideration could be given to intensified anticoagulation therapy, although the benefits or risks of such an approach are unknown. Vigilance and early investigation and treatment of macrothrombotic complications are recommended.[44]

Stable patients who are considered well enough for discharge home from the emergency department are less likely to have ongoing thromboinflammation. There have been no studies reporting the use of parameters such as D-dimer to predict outcomes in such patients, and the incidence of VTE is unknown. Presently, no risk stratification tools exist to identify patients who would benefit from thromboprophylaxis at home. Home thromboprophylaxis would also be complicated by either the need for injectable low-molecular weight heparin (LMWH) or concerns regarding potential drug interactions between direct oral anticoagulants and azithromycin (P-gp inhibition) or investigational antiviral medications (such as lopinavir/ritonavir).[43] At the current time, we believe that it is preferable to advise return to the emergency department in the case of worsening pneumonia symptoms to facilitate hospital admission and thromboprophylaxis. There are insufficient data to suggest thromboprophylaxis for outpatients or for postdischarge patients with COVID-19. However, guidance from the American College of Cardiology recommends considering extended prophylaxis (up to 45 days) for discharged COVID-19 patients at increased risk of VTE (immobility, medical comorbidities such as cancer, and persistently elevated D-dimer levels).[43,44]

Risk Stratification Based on Coagulopathy

In an interim guide from ISTH, Thachil et al.[41] suggest early risk stratification for admission and thromboprophylaxis based on D-dimer, prothrombin time, platelet count, and fibrinogen level. Because of the insensitivity and lack of rapidly available measures of fibrinolysis, viscoelastic testing may be helpful for rapid stratification of COVID-19 patients based on hypercoagulability because these tests may be completed in an hour. Viscoelastic testing, including thromboelastography and rotational thromboelastometry have been of benefit for predicting organ failure[45] and DIC in patients with sepsis.[46] Viscoelastic testing is now being investigated for predicting hypercoagulability in COVID-19 patients. From two studies in critically ill COVID-19 ICU patients in Italy, these patients appear to be hypercoagulable.[7,30]

Early prognostication using the ISTH SIC score may prevent progression toward overt DIC. The ISTH Scientific Standardization

Committee has proposed a new category of SIC that encompasses the acute phase of infection to identify earlier therapeutic points that may prevent progression toward fulminant DIC.[21] Nonsurvivors go on to develop overt DIC, with up to 71% of patients meeting the ISTH diagnostic criteria for overt-DIC (≥5 points) in the later stages of infection.[31] In the 183-patient series, only 1 person who met the criteria for DIC survived. Understanding the timing and association of coagulation parameters in the course of COVID-19 infection may yield important markers for earlier treatment of thrombosis to lower the burden of critical illness.[40]

Salvage and Experimental Therapies for the Critically Ill

There have been promising animal and phase I studies looking at the role of thrombolysis in ALI.[47–49] Fibrinolytic treatment of microvascular thrombosis in COVID-19 ARDS may emerge as a salvage therapy because of ALI-induced clot formation and fibrinolysis suppression.[50] One group has proposed low-dose tPA salvage therapy for patients with COVID-19 ARDS who fail to oxygenate despite ventilator support and prone-positioning and are not candidates for extracorporeal membrane oxygenation (ECMO). In three such patients, tPA administration resulted in improved oxygenation.[51] A phase IIa study evaluating the efficacy and safety of intravenous tPA is underway (NCT04357730).

Directly targeting immunothrombosis through degradation of excess NETs from neutrophils is reviewed by Barnes et al.[24] Acute respiratory distress syndrome and microthromboses are linked to NETopathies, and drugs inhibiting NET formation have been investigated in clinical trials.[52] A recombinant inhaled DNase I (dornase alfa) has been shown to dissolve NETs and clear mucus in the airways of CF patients.[53]

Recombinant activated protein C (aPC; drotrecogin α) was briefly approved as a therapy for sepsis but was withdrawn from the market because of concerns about bleeding and lack of mortality reduction.[54,55] Subgroup analyses of trials supporting the use of aPC in severe sepsis suggest that patients with severe ARDS from pneumonia had a mortality benefit,[56] which may be a promising lead for its use in COVID-19 pneumonia. A recombinant aPC variant with normal EPCR and PAR1 signaling and low anticoagulant activity has been developed and reduces mortality in animal models of sepsis.[57] Soluble thrombomodulin has received support for sepsis-induced DIC in Japan and, unlike aPC, may have a lower potential for bleeding due to thrombomodulin's antifibrinolytic activity.[58,59]

SUMMARY

Coronavirus disease 2019–associated coagulopathy is emerging as a potential target for intervention in SARS-CoV-2–related illness. Many questions remain in the targeting of inflammation, coagulation, and fibrinolysis in these patients.

AUTHORSHIP

C.H.Y. wrote the article. C.H.Y., N.V., and P.Y.K. generated the figure. K.d.W., J.H.L., J.I.W., P.C.L., A.F.-R., K.S., and P.Y.K. critically edited the article.

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REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [published online February 24, 2020]. *JAMA*. 2020. doi:10.1001/jama.2020.2648.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)*. 2020;395(10229):1054–1062.
4. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. Published online February 28, 2020.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. Published online February 7, 2020.
6. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020;382(17):e38. Published online April 8, 2020.
7. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, Falco M, Albano G, Menicanti L. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747–1751. Published online May 6, 2020: jth.14854.
8. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8(7):681–686.
9. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, Mauad T, Marcia Negri E. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost*. 2020;18(6):1517–1519. Published online April 15, 2020.
10. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med*. 2020;173(4):268–277. Published online May 6, 2020.
11. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19: a prospective cohort study. *J Thromb Haemost*. Published online April 17, 2020:jth.14849.
12. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421–1424. Published online April 9, 2020.
13. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. Published online April 2020.
14. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089–1098.
15. Chen J, Wang X, Zhang S, et al. Findings of acute pulmonary embolism in CO-VID-19 patients. Available at: https://sfar.org/the-lancet-infectious-diseases-findings-of-acute-pulmonary-embolism-in-covid-19-patients/. Accessed August 3, 2020.

16. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol*. 2020;15(5):700–704. Published online February 28, 2020.
17. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol*. 2020;94(7):e00127–e00120.
18. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J*. 2020;55(4):2000607.
19. Yang Y, Tang H. Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. *Cell Mol Immunol*. 2016;13(4):432–442.
20. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care*. 2017;7(1):117.
21. Iba T, Levy JH, Raj A, Warkentin TE. Advance in the management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Clin Med*. 2019;8(5).
22. Ito T. PAMPs and DAMPs as triggers for DIC. *J Intensive Care*. 2014;2(1):67.
23. Liaw PC, Ito T, Iba T, Thachil J, Zeerleder S. DAMP and DIC: the role of extracellular DNA and DNA-binding proteins in the pathogenesis of DIC. *Blood Rev*. 2016;30(4):257–261.
24. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J Exp Med*. 2020;217(6).
25. Ouyang Y, Wang Y, Liu B, Ma X, Ding R. Effects of antiplatelet therapy on the mortality rate of patients with sepsis: a meta-analysis. *J Crit Care*. 2019; 50:162–168.
26. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in COVID-19 patients [published online June 23, 2020]. *Blood*. doi:10.1182/blood.2020007214.
27. Toltl LJ, Austin RC, Liaw PC. Activated protein C modulates inflammation, apoptosis and tissue factor procoagulant activity by regulating endoplasmic reticulum calcium depletion in blood monocytes. *J Thromb Haemost*. 2011;9(3):582–592.
28. Iba T, Thachil J. Clinical significance of measuring plasminogen activator inhibitor-1 in sepsis. *J Intensive Care*. 2017;5:56, 56.
29. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. 2020;20(5):269–270. Published online April 9, 2020.
30. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738–1742. Published online April 17, 2020: jth.14850.
31. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844–847.
32. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;58(7):1116–1120. Published online March 16, 2020.
33. 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;395(10223):507–513.
34. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost*. 2020;18(6):1324–1329. Published online April 19, 2020: jth.14859.
35. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med*. 2017;377(6):562–572.
36. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress [published online april 24, 2020]. *JAMA*. 2020. doi:10.1001/jama.2020.6825.
37. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46(6):1099–1102. Published online April 14, 2020.
38. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1–13. Published online April 2020.
39. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*. 2020;1–4. Published online April 3, 2020.
40. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol*. 2020;76(1):122–124. Published online May 2020.
41. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023–1026. Published online March 25, 2020.
42. American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions. Available at: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation. Accessed August 3, 2020.
43. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020;75(23):2950–2973. Published online April 2020.
44. 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;18(8):1859–1865. Published online May 27, 2020: jth.14929.
45. Prakash S, Verghese S, Roxby D, Dixon D, Bihari S, Bersten A. Changes in fibrinolysis and severity of organ failure in sepsis: a prospective observational study using point-of-care test—ROTEM. *J Crit Care*. 2015;30(2):264–270.
46. Koami H, Sakamoto Y, Ohta M, et al. Can rotational thromboelastometry predict septic disseminated intravascular coagulation? *Blood Coagul Fibrinolysis*. 2015;26(7):778–783.
47. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia—a review. *Crit Care Med*. 2006;34(3):871–877.
48. Liu C, Ma Y, Su Z, et al. Meta-analysis of preclinical studies of fibrinolytic therapy for acute lung injury. *Front Immunol*. 2018;9:1898.
49. Hardaway RM, Harke H, Tyroch AH, Williams CH, Vazquez Y, Krause GF. Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. *Am Surg*. 2001;67(4):377–382.
50. Moore HB, Barrett CD, Moore EE, McIntyre RC, Moore PK, Talmor DS, Moore FA, Yaffe MB. Is there a role for tissue plasminogen activator as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome. *J Trauma Acute Care Surg*. 2020;88(6):713–714. Published online March 2020: 1.
51. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, Yaffe MB, Moore HB, Barrett CD. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. 2020;18(7):1752–1755. Published online April 8, 2020.
52. Tagami T, Tosa R, Omura M, et al. Effect of a selective neutrophil elastase inhibitor on mortality and ventilator-free days in patients with increased extravascular lung water: a post hoc analysis of the PiCCO Pulmonary Edema Study. *J Intensive Care*. 2014;2(1):67.
53. Papayannopoulos V, Staab D, Zychlinsky A. Neutrophil elastase enhances sputum solubilization in cystic fibrosis patients receiving DNase therapy. *PLoS One*. 2011;6(12):e28526.
54. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10): 699–709.
55. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.
56. Laterre P-F, Garber G, Levy H, Wunderink R, Kinasewitz GT, Sollet J-P, Maki DG, Bates B, Yan SCB, Dhainaut J-F. Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. *Crit Care Med*. 2005;33(5):952–961.
57. Kerschen EJ, Fernandez JA, Cooley BC, Yang XV, Sood R, Mosnier LO, Castellino FJ, Mackman N, Griffin JH, Weiler H. Endotoxemia and sepsis mortality reduction by non-anticoagulant activated protein C. *J Exp Med*. 2007;204(10):2439–2448.
58. Saito H, Maruyama I, Shimazaki S, et al. Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost*. 2007;5(1):31–41.
59. Yamakawa K, Murao S, Aihara M. Recombinant human soluble thrombomodulin in sepsis-induced coagulopathy: an updated systematic review and meta-analysis. *Thromb Haemost*. 2019;119(1):56–65.