Published online: 2020-06-04

Coagulopathy in COVID-19 and Its Implication for Safe and Efficacious Thromboprophylaxis

Florian Langer[1] Stefan Kluge[2] Robert Klamroth[3] Johannes Oldenburg[4]

[1] Zentrum für Onkologie, II. Medizinische Klinik und Poliklinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
[2] Klinik für Intensivmedizin, Zentrum für Anästhesiologie und Intensivmedizin, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
[3] Zentrum für Gefäßmedizin, Klinik für Innere Medizin – Angiologie und Hämostaseologie, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[4] Institut für Experimentelle Hämatologie und Transfusionsmedizin, Universitätsklinik Bonn, Bonn, Germany

Address for correspondence Florian Langer, Prof. Dr. med., Zentrum für Onkologie, II. Medizinische Klinik und Poliklinik, Universitätsklinikum Eppendorf, Martinistr. 52, D-20246 Hamburg, Germany (e-mail: langer@uke.de).

Hämostaseologie 2020;40:264–269.

Abstract

The novel coronavirus, SARS-CoV-2, is causing a global pandemic of life-threatening multiorgan disease, called COVID-19. Accumulating evidence indicates that patients with COVID-19 are at significant risk of thromboembolic complications, mainly affecting the venous, but also the arterial vascular system. While the risk of venous thromboembolism (VTE) appears to be higher in patients requiring intensive care unit support compared to those admitted to general wards, recent autopsy findings and data on the timing of VTE diagnosis relative to hospitalization clearly suggest that thromboembolic events also contribute to morbidity and mortality in the ambulatory setting. In addition to a severe hypercoagulable state caused by systemic inflammation and viral endotheliitis, some patients with advanced COVID-19 may develop a coagulopathy, which meets established laboratory criteria for disseminated intravascular coagulation, but is not typically associated with relevant bleeding. Similar to other medical societies, the Society of Thrombosis and Haemostasis Research has issued empirical recommendations on initiation, dosing, and duration of pharmacological VTE prophylaxis in COVID-19 patients.

Keywords

- COVID-19
- deep vein thrombosis
- pulmonary embolism
- coagulopathy

Zusammenfassung

Das neue Coronavirus SARS-CoV-2 ist für eine weltweite Pandemie der lebensbedrohlichen Multiorganerkrankung COVID-19 verantwortlich. Zahlreiche Fallserien und Beobachtungsstudien zeigen, dass betroffene Patienten ein erhebliches Risiko für Thromboembolien aufweisen, die vor allem das venöse, jedoch auch das arterielle Gefäßsystem betreffen. Während das Risiko für eine venöse Thromboembolie (VTE) bei Intensivpatienten höher zu sein scheint als bei Patienten auf der Normalstation, deuten aktuelle Obduktionsbefunde und Analysen des zeitlichen Zusammenhangs zwischen VTE-Diagnose und Krankenhausaufnahme darauf hin, dass Thromboembolien auch im ambulanten Bereich signifikant zur Morbidität und Mortalität beitragen. Zusätzlich zur

received
May 13, 2020
accepted
May 14, 2020

DOI https://doi.org/10.1055/a-1178-3551.
ISSN 0720-9355.

Schlüsselwörter
- COVID-19
- Beinvenenthrombose
- Lungenembolie
- Koagulopathie

Hyperkoagulabilität, hervorgerufen durch Entzündung und virale Endotheliitis, entwickeln einige Patienten mit fortgeschrittener Erkrankung eine Koagulopathie, die die Laborkriterien einer disseminierten intravasalen Gerinnung erfüllt, jedoch selten mit einer Blutungsneigung einhergeht. Wie andere Fachgesellschaften hat auch die GTH e.V. empirische Empfehlungen zur Indikationsstellung, Dosierung und Dauer einer medikamentösen VTE-Prophylaxe bei COVID-19 formuliert.

Introduction

Emerging evidence from China and other countries indicates that infection with the novel coronavirus, SARS-CoV-2, which causes a potentially life-threatening disease of the upper and lower airways called COVID-19, is associated with significant activation of the coagulation system. This "coagulopathy" may result in vascular complications, mainly venous thromboembolism (VTE), a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE), which have significant implications for the clinical outcome of COVID-19 patients.[1–5] Anticoagulant strategies to prevent or treat VTE in ambulatory and hospitalized patients with proven SARS-CoV-2 infection have thus gained tremendous attention over the last weeks and months. Recently, a number of national and international medical societies, including the Society of Thrombosis and Haemostasis Research (GTH—Gesellschaft für Thrombose- und Hämostaseforschung e.V.), have published recommendations on thromboprophylaxis and management of COVID-19-associated coagulopathy.[6–11]

Evidence from Mainland China

In February 2020, colleagues from Wuhan, China, reported on abnormal coagulation parameters in 183 consecutive COVID-19 patients.[3] Baseline levels of prothrombin time (PT), D-dimer, and fibrin degradation products were significantly increased in nonsurvivors ($n = 21$) compared to survivors ($n = 162$). Moreover, 71.4% of patients with a fatal outcome developed a progressive systemic coagulopathy over the course of hospitalization, which was consistent with overt disseminated intravascular coagulation (DIC) according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH), while this was the case in only 0.6% of surviving patients. Median time to DIC was 4 days (range: 1–12 days). At later stages, DIC in nonsurvivors was characterized by massively elevated D-dimer and fibrinogen consumption, a finding consistent with excessive fibrinolysis. Unfortunately, no further information was provided, e.g., on anticoagulant treatment strategies or on whether patients with a fatal outcome had suffered from septic shock due to bacterial superinfection or had received intensive life support measures such as extracorporeal membrane oxygenation (ECMO) therapy.

In another study from China involving 191 COVID-19 patients, 50% of those who died presented with a coagulopathy, as defined by a 3-second prolongation of the PT and/or a 5-second prolongation of the activated partial thromboplastin time (APTT), while this was the case in only 7% of surviving patients ($p < 0.0001$).[12] A baseline D-dimer level of >1 mg/L was associated with an 18-fold increased risk of death, with D-dimer levels progressively increasing over the course of hospitalization in nonsurvivors.

Tang and coworkers retrospectively investigated the effect of prophylactic anticoagulation, mainly with low-molecular-weight heparin (LMWH), on 28-day mortality in a cohort of 449 patients with severe COVID-19 from Wuhan.[13] Ninety-nine patients (22.0%) had received pharmacological thromboprophylaxis for ≥7 days, and 97 patients (21.6%) had developed septic-induced coagulopathy (SIC), as defined by the criteria of low platelet counts, prolonged PT, and sepsis-related organ failure assessment score. Heparin prophylaxis (vs. no heparin prophylaxis) had no effect on survival in the total patient cohort, with 28-day mortality rates of 30.3 versus 29.7%, respectively ($p = 0.910$), but significantly decreased 28-day mortality in patients with SIC (40.0 vs. 64.2%, $p = 0.029$) or in those with a baseline D-dimer level of >3 mg/L (32.8 vs. 52.4%, $p = 0.017$).The ISTH interim guidance on recognition and management of coagulopathy in COVID-19 recommends prophylactic anticoagulation with LMWH in all hospitalized patients, regardless of the presence of SIC or DIC.[6]

Following initial case reports on PE in COVID-19 patients,[14] a retrospective study from Wuhan analyzed the frequency of venous thrombosis of the lower extremities, as detected by screening Doppler ultrasonography, in a cohort of 81 patients admitted to an intensive care unit (ICU).[15] The authors reported a thrombosis prevalence of 25% (20/81 patients) with no further information provided regarding the type (superficial vein thrombosis vs. DVT) and localization (distal vs. proximal or unilateral vs. bilateral venous thrombosis). In this study, pharmacological thromboprophylaxis was not routinely administered. A baseline D-dimer cut-off value of 1.5 mg/L resulted in 85% sensitivity and a negative predictive value of 95% for the detection of lower extremity venous thrombosis, which was also associated with advanced patient age and decreased lymphocyte counts.

Evidence from Europe and North America

When interpreting findings of case series and observational studies from China, it is important to consider ethnicity, which has a significant impact on the thrombotic risk. In epidemiological studies, the incidence of VTE was three- to four-fold lower in Chinese compared to Caucasian individuals, while the VTE risk in African Americans appears to be higher than that in Caucasians.[16–18]

In an Irish cohort of 83 COVID-19 patients, mainly of Caucasian ethnicity, baseline D-dimer levels were significantly increased in patients with a fatal outcome and/or

requiring ICU admission ($n = 33$) compared to surviving non-ICU patients ($n = 50$).[5] While there was no difference in platelet counts and PT and APTT values, levels of fibrinogen and C-reactive protein (CRP) were significantly increased in patients with a nonfavorable outcome. None of the patients initially presented with overt DIC according to ISTH criteria, and none of the patients maintained on LMWH prophylaxis developed overt DIC over the course of hospitalization.

In three Dutch hospitals, there was a 31% cumulative incidence of thromboembolic complications in 184 COVID-19 patients treated in an ICU over a median observation period of 7 days (interquartile range: 1–13 days).[4] Importantly, all patients had received standard VTE prophylaxis with LMWH, and no imaging studies had been performed to screen for VTE. PE was the most frequent thrombotic complication, accounting for 25 of the 31 events, while three patients had experienced acute ischemic stroke.

Comparing 75 ICU with 123 non-ICU COVID-19 patients admitted to the Amsterdam University Academic Medical Center, Middeldorp et al. found a significantly increased proportion of patients with symptomatic or asymptomatic VTE in the ICU (47.0%) compared to the non-ICU cohort (3.3%), with cumulative VTE incidence rates in ICU patients of 26, 47, and 59% at 7, 14, and 21 days, respectively.[19] These VTE rates were observed despite prophylactic anticoagulation being the standard of care for all patients included in the study. During the study period, ICU patients began to receive a double dosage of anticoagulation, compared to patients treated in general wards. The risk of VTE in ICU patients was not lower in the period in which the anticoagulation dosage was doubled (58%) than in the initial study period (41%).

Working groups from France also reported high frequencies of VTE in COVID-19 patients requiring ICU admission.

In 26 mechanically ventilated patients, screening duplex and Doppler ultrasonography of the lower extremities revealed superficial vein thrombosis or DVT in 4 and 14 patients, respectively, with bilateral thrombosis being present in 10 patients.[20] The frequency of thrombosis was significantly higher in patients receiving prophylactic (8/8 patients) as compared to those receiving therapeutic anticoagulation (10/18 patients, $p = 0.03$). Computed tomography pulmonary angiography (CTPA) or transesophageal echocardiography was performed in cases of persistent or secondary respiratory failure and detected PE in six patients, all of whom had received therapeutic anticoagulation.

In another French study involving 107 ICU patients with COVID-19, PE was diagnosed by CTPA in 22 patients (20.6%).[21] This rate appeared higher when compared to the PE rate of a historical control group of 196 ICU patients (6.1%) or a group of 40 patients with influenza viral pneumonia (7.5%). Importantly, CTPA was ordered more frequently in the influenza viral pneumonia (42.5%) than in the COVID-19 patient cohort (31.8%).

A similar finding was obtained when 77 patients with COVID-19-associated acute respiratory distress syndrome (ARDS) were matched with 145 patients suffering from non-COVID-19 ARDS.[22] The rate of PE was significantly higher in COVID-19 compared to non-COVID-19 ARDS patients (11.7 vs. 2.1%, $p = 0.01$).

Evaluating the usefulness of plasma D-dimer in providing guidance on whether or not to order imaging studies, a level of >2.66 mg/L was found to have 100% sensitivity and 67% specificity for the detection of PE by CTPA.[23]

Recent autopsy data from 12 consecutive COVID-19-positive deaths in Hamburg, Germany, revealed bilateral DVT in seven patients (58%) and massive, fatal PE in four patients (33%), with thrombi deriving from the deep veins of the lower extremities.[24] In addition, thrombosis of the prostatic venous plexus was diagnosed in six of the nine men. In none of the patients, VTE was suspected before death. Importantly, two patients died from massive PE outside the hospital, suggesting that COVID-19 is associated with a significant risk of VTE even in the ambulatory setting.

Consistent with these findings, Lodigiani et al. found that 50% of all VTE events recorded in 362 hospitalized COVID-19 patients from Milan, Italy, were diagnosed within 24 hours after hospital admission.[25]

In a retrospective study involving 2,773 hospitalized COVID-19 patients from New York City, United States, administration of treatment dose anticoagulation was associated with decreased in-hospital mortality, particularly in patients requiring mechanical ventilation.[26]

Pathophysiological Considerations

The pathophysiological mechanisms leading to severe COVID-19 and the role of the hemostatic system in disease progression are not yet fully understood. The lung seems to be the target organ for SARS-CoV-2, and patients may develop acute lung injury and ARDS upon infection. However, increasing evidence emerges that severe COVID-19 is a multiorgan disease associated with a coagulopathic state.[27] In the German autopsy study, viral RNA titers were also detected in other organs such as the liver, kidney, or heart.[24]

In general, microorganisms can activate monocytes, tissue macrophages, and endothelial cells, thus triggering the production of proinflammatory cytokines and activation of the coagulation protease cascade. Both, inflammation and coagulation, are synchronous responses of the host's defense aimed at containing invading pathogens. These complex processes are referred to as thrombo-inflammation or immunothrombosis. The loss of normal antithrombotic and anti-inflammatory functions of endothelial cells leads to dysregulation of coagulation, platelet activation, and leukocyte recruitment in the microvasculature, with complement activation likely playing an important role in the context of COVID-19-associated pneumonitis and purpuric skin lesions.[28–30]

To describe the coagulation changes in COVID-19 patients, the term CAC (COVID-19-associated coagulopathy) has been introduced.[27] Coagulation test abnormalities in the early phase of SARS-CoV-2 infection do not result in clinical bleeding and thus do not fulfill the more stringent definition of "coagulopathy." Whether progression of initial coagulation changes to SIC or DIC is a characteristic feature of COVID-19 and not caused, e.g., by ARDS, septic shock, or ECMO therapy is currently not

clear. Even in COVID-19 patients with overt DIC, bleeding manifestations have not been reported.[27] To differentiate the changes of hemostatic parameters observed in COVID-19 patients from those observed in patients with DIC and consumptive coagulopathy of other etiologies, the term pulmonary intravascular coagulopathy (PIC) has been introduced.[5] Studies using viscoelastic whole blood assays have demonstrated significant hypercoagulability due to a severe inflammatory state in COVID-19 patients requiring ICU admission,[31,32] further arguing against DIC as a universal finding in advanced disease stages. Thus, the designations CAC or PIC have been introduced in COVID-19 patients to underline that their laboratory (and clinical) hemostasis features are distinct from overt DIC. Neither CAC nor PIC, however, are currently well defined.

In some patients with COVID-19, a prolonged APTT, which is frequently considered indicative of a systemic "coagulopathy," may actually be caused by a lupus anticoagulant,[33] thus conferring an increased thrombotic rather than an increased hemorrhagic risk. Whether elevated antiphospholipid antibodies play a role in the pathogenesis of COVID-19-associated thromboembolic complications and coagulation activation[34,35] warrants further investigation.

The tropism of SARS-CoV-2 for angiotensin converting enzyme 2 receptors expressed on endothelial cells seems to result in endothelial cell activation and apoptosis. There is evidence for direct infection of endothelial cells not only in the lungs, but also in the kidneys or the small intestine with consecutive infiltration of mononuclear leukocytes and both endothelial and inflammatory cell death.[36] Signs of endothelial activation in severe COVID-19 infection have been described with massively elevated plasma levels of von Willebrand factor and factor VIII.[34]

Elevated levels of interleukin-6 (IL-6), CRP, erythrocyte sedimentation rate, and fibrinogen indicate systemic inflammation in patients with COVID-19. The inflammation is the probable cause for elevated D-dimer levels, and may also be a sign of acute lung injury. Thus, D-dimer levels track the severity of disease progression and inflammation. A hyperinflammatory response arises in some patients, resulting in a cytokine storm and dramatic changes in coagulation tests, including elevated D-dimers. Increases of IL-6 levels have been reported to correlate with increased fibrinogen levels, confirming the link between inflammation and procoagulant changes of the hemostatic system.[27]

Some COVID-19 patients develop severe hypoxemia, and thrombus formation is increased under hypoxic conditions. The vascular response to hypoxia is primarily controlled by hypoxia-induced transcription factors, targeting genes responsible for regulation of thrombus formation.[37]

Taken together, inflammation and hypoxia in COVID-19 lead to a prothrombotic state, which is usually not in accordance with the ISTH definition of overt DIC. Evolution of a systemic coagulopathy is indicative of a poor prognosis. It should be considered that COVID-19 patients may be immobile for a while before hospitalization. Further risk factors such as advanced age, comorbidities, and history of VTE may result in thromboembolic complications even after successful treatment of the SARS-CoV-2 infection and discharge from hospital.

VTE Prophylaxis in COVID-19

Based on the current literature and according to similar guidance documents from other medical societies, the GTH e.V. has issued the following recommendations on VTE prophylaxis in patients with SARS-CoV-2 infection (COVID-19).[11] Further adaption of these recommendations will be necessary with increasing knowledge of the disease.

- In all patients with confirmed SARS-CoV-2 infection, the indication for pharmacological VTE prophylaxis with LMWH (or alternatively with fondaparinux) should be evaluated on a regular and permissive basis, regardless of the need for hospitalization.
- If pharmacological VTE prophylaxis is indicated, LMWH should be given at a dosage approved for high-risk situations. In case of contraindications for anticoagulation, physical measures should be used (e.g., medical compression stockings).
- Levels of plasma D-dimers should be determined in symptomatic patients with confirmed SARS-CoV-2 infection. In the case of significantly elevated D-dimer levels ($\geq$1.5–2.0 mg/L), pharmacological VTE prophylaxis should be initiated and hospitalization be considered, regardless of the severity of clinical symptoms.
- All hospitalized COVID-19 patients should receive pharmacological VTE prophylaxis in the absence of contraindications.
- Intensified VTE prophylaxis (e.g. with an intermediate, half-therapeutic LMWH dosage once daily or with a high-risk prophylactic LMWH dosages twice daily) should be considered in patients with additional risk factors (e.g. body mass index $> 30\ kg/m^2$, history of VTE, known thrombophilia, active cancer) and/or requiring ICU admission and/or with rapidly increasing D-dimer levels, taking into account renal function and bleeding risk.
- In the absence of confirmed VTE or ECMO therapy, anticoagulation at treatment dosages can currently not be recommended on a routine basis. In cases of suspected VTE (e.g., acute deterioration of dyspnea, unexplained decrease in oxygen saturation, progressive peripheral edema, rapid increase of plasma D-dimers), appropriate imaging studies (CTPA, ultrasonography) should be ordered permissively.
- Hemostatic parameters should be monitored in all hospitalized patients with SARS-CoV-2 infection. Reasonable parameters are D-dimers, PT/international normalized ratio, platelet count, fibrinogen, and antithrombin.
- Thrombocytopenia and/or a prolonged APTT or PT without clinical signs of bleeding are *per se* no contraindications for pharmacological VTE prophylaxis.
- In ECMO-treated patients receiving unfractionated heparin, laboratory monitoring should target for 1.5- to 1.8-fold prolongation of the baseline APTT. In cases of severe inflammation with "heparin resistance," additional monitoring of anti-Xa activity levels (target range: 0.3–0.7 IU/mL) is recommended.

- Following discharge from hospital, prolonged pharmacological VTE prophylaxis in the ambulatory setting is reasonable in patients with persistent immobility, high inflammatory activity, and/or additional risk factors (as mentioned above). The recommendation for prolonged VTE prophylaxis, at the initially prescribed dosage, should be communicated to general practitioners in discharge documents and reviewed by a hematologist or vascular specialist.

In hospitalized COVID-19 patients who develop VTE, especially in those requiring ICU admission, LMWH at therapeutic dosages may be considered the standard of care. In cases of severe renal insufficiency, unfractionated heparin should be administered. Anticoagulation for VTE should be continued for 3 to 6 months. In the ambulatory setting, oral anticoagulation, including treatment with direct oral anticoagulants, is feasible. Bleeding risk and potential pharmacological interactions with other medications in patients with multiple comorbidities must be considered.

Perspective

With a plethora of studies delineating the highly thrombogenic state in COVID-19 patients and suggesting that standard prophylactic dosages of LMWH may not be sufficient in all cases, results from rigorously conducted trials are eagerly awaited. A number of clinical studies have been initiated to answer important questions such as the following: Is very early prophylactic anticoagulation beneficial with regard to prevention of VTE and other relevant endpoints, e.g., hospitalization, need for ICU admission, mortality? Is intensified anticoagulation with intermediate or full therapeutic dosages required to protect hospitalized patients from VTE? Who will benefit from prolonged pharmacological VTE prophylaxis following hospital discharge? These questions require valid answers to modify or intensify the current anticoagulation management of COVID-19 patients accordingly.

Conflicts of Interest

F.L. has received personal fees for lectures or consultancy and/or research support from Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, CSL Behring, Daiichi Sankyo, LEO Pharma, Pfizer, Roche, Sanofi, SOBI, and Takeda.

S.K. has received personal fees for lectures or consultancy and/or research support from Ambu, AMOMED, ArjoHuntleigh, Astellas, Astra, Bard, Basilea, Baxter, Bayer, Biotest, CSL Behring, Cytosorbents, E.T.ViewLtd, Fisher & Paykel, Fresenius, Gilead, MSD, Orion, Pfizer, Philips, Sedana, Sorin, Xenios, and Zoll.

R.K. has received personal fees for lectures or consultancy and/or research support from Bayer, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, LEO Pharma, Pfizer, Sanofi, and Takeda.

J.O. has received personal fees for lectures or consultancy and/or research support from Bayer, Biogen Idec, Biotest, Chugai, CSLBehring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, SOBI, and Takeda.

References

1 Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720
2 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
3 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost 2020;18(04):844–847
4 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 (e-pub ahead of print) . Doi: 10.1016/j.thromres.2020.04.013
5 Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020 (e-pub ahead of print) . Doi: 10.1111/bjh.16749
6 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J ThrombHaemost 2020;18(05):1023–1026
7 Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. 2020;18(03):167–169
8 Alessandro C, Alberio L, Angelillo-Scherrer A, et al. Suggestions for thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19. Swiss Med Wkly 2020;150:w20247
9 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 (e-pub ahead of print) . Doi: 10.1016/j.jacc.2020.04.031
10 Deutsche Gesellschaft für Angiologie (DGA). COVID-19-Infektion und Risiko für thromboembolische Komplikationen. Available at: www.dga-gefaessmedizin.de. Accessed April 27, 2020
11 Gesellschaft für Thrombose- und Hämostaseforschung e. V. Aktualisierte Empfehlungen zur Thromboseprophylaxe bei SARS-CoV2 (COVID-19). Available at: www.gth-online.de. (April 21, 2020
12 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 2020;395 (10229):1054–1062
13 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020;18(05):1094–1099
14 Xie Y, Wang X, Yang P, et al. COVID-19 complicated by acute pulmonary embolism. Cardiothorac Imaging 2020;2(02):e200067
15 Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J ThrombHaemost 2020 (e-pub ahead of print) . Doi: 10.1111/jth.14830
16 Liao S, Woulfe T, Hyder S, Merriman E, Simpson D, Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. J ThrombHaemost 2014;12(02):214–219
17 White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009;123 (123, Suppl 4):S11–S17
18 Huang D, Wong E, Zuo ML, et al. Risk of venous thromboembolism in Chinese pregnant women: Hong Kong venous thromboembolism study. Blood Res 2019;54(03):175–180
19 Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost 2020 (e-pub ahead of print) . Doi: 10.1111/jth.14888
20 Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J ThrombHaemost 2020 (e-pub ahead of print) . Doi: 10.1111/jth.14869

21 Poissy J, Goutay J, Caplan M, et al; Lille ICU Haemostasis COVID-19 Group. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation 2020 (e-pub ahead of print) . Doi: 10.1161/CIRCULATIONAHA.120.047430

22 Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 May 4;1–10. (e-pub ahead of print). Doi: 10.1007/s00134-020-06062-x

23 Leonard-Lorant I, Delabranche X, Severac F, et al. Acute pulmonary embolism in COVID-19 patients on CT angiography and relationship to D-dimer levels. Radiology 2020 (e-pub ahead of print) . Doi: 10.1148/radiol.2020201561

24 Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020 (e-pub ahead of print) . Doi: 10.7326/M20-2003

25 Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14

26 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 (e-pub ahead of print) . Doi: 10.1016/j.jacc.2020.05.001

27 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020 (e-pub ahead of print) . Doi: 10.1182/blood.2020006000

28 Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J ThrombHaemost 2018;16(02): 231–241

29 Jackson SP, Darbousset R, Schoenwaelder SM. Thrombo-inflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 2019;133(09): 906–918

30 Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19infection: a report of five cases. Trans Res 2020 (e-pub ahead of print) . Doi: 10.1016/j.trsl.2020.04.007

31 Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. J ThrombHaemost 2020 (e-pub ahead of print) . Doi: 10.1111/jth.14850

32 Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J ThrombHaemost 2020 (e-pub ahead of print) . Doi: 10.1111/jth.14854

33 Bowles L, Platton S, Yartey N, et al. Lupus anticoagulant and abnormal coagulation tests in patients with COVID-19. N Engl J Med 2020 (e-pub ahead of print) . Doi: 10.1056/NEJMc2013656

34 Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res 2020;190:62

35 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

36 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234):1417–1418

37 Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019;181:77–83