

Venous Thrombosis and SARS-CoV-2

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Abstract

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection is associated with high risk of venous and arterial thrombosis. Thrombotic complications, especially pulmonary embolism, lead to increased all-cause mortality in both intensive care unit and noncritically ill patients. Damage and activation of vascular endothelium, platelet activation, followed by thrombotic and fibrinolytic imbalance as well as hypercoagulability are the key pathomechanisms in immunothrombosis leading to a significant increase in thromboembolism in coronavirus disease 2019 (COVID-19) compared with other acute illnesses. In this review article, we discuss the incidence and prognosis, diagnosis, prevention, and treatment of venous thromboembolism in patients with COVID-19 disease, based on clinical experience and research available to date.

Keywords

- ▶ SARS-CoV-2
- ▶ COVID-19
- ▶ thrombosis
- ▶ venous thromboembolism

Zusammenfassung

COVID-19 ist mit einem erhöhten Risiko venöser bzw. arterieller Thrombosen assoziiert. Im Rahmen einer SARS-CoV-2 Infektion resultieren thromboembolische Komplikationen, vor allem die Lungenarterienembolie, in einer erhöhten Mortalität. Im Vergleich zu anderen akuten Krankheitsbildern führt COVID-19 zu Endothelschäden sowie Thrombozytenaktivierung und begünstigt ein Missverhältnis zwischen Thrombose und Fibrinolyse mit konsekutiv gesteigerter Thrombogenität. Dieser Artikel bietet einen aktuellen Überblick über die Diagnostik, Behandlung, Prognose sowie Prävention von thromboembolischen Komplikationen im Rahmen einer SARS-CoV-2 Infektion.

Schlüsselwörter

- ▶ SARS-Cov2
- ▶ COVID-19
- ▶ Thrombose
- ▶ venöse Thromboembolie

Clinical Case of Venous Thromboembolism in a COVID-19 Patient

A 68-year-old patient with fatigue, nausea, and vomiting presented at the emergency department. The patient had a history of chronic coronary syndrome with normal systolic left ventricular ejection fraction after an ST-elevation myocardial infarction 4 years ago. Due to hypoxemia (initial oxygen saturation <85%), leukocytosis, and elevated C-reactive protein (CRP; 10.25 mg/dL) with a low procalcitonin (0.19 ng/mL), a viral respiratory pneumonia was suspected. The patient could be stabilized via noninvasive ventilation and soon tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Due to highly elevated plasma concentrations of D-dimer, a computed tomography pulmonary angiography (CTPA) was performed and revealed embolism of the right pulmonary artery as well as left segmental pulmonary arteries (▶ Fig. 1A). To detect the source of embolism, a compression ultrasonography was performed and revealed a deep vein thrombosis (DVT) of the right lower extremity. Due to advanced age, no screening of thrombophilia was performed. It was, however, recommended to perform a tumor screening after discharge.

No opacities typical for COVID-19 could be detected initially; however, bilateral mostly right-sided pulmonary consolidations developed later (▶ Fig. 1B). Bacterial pneumonia could not be ruled out; therefore, empirical antimicrobial therapy was initiated.

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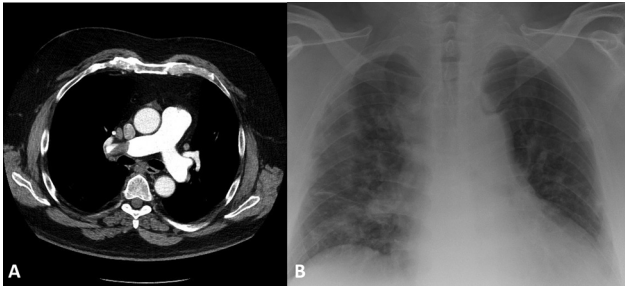


Fig. 1 (A) Thrombi in the right pulmonary artery and left segmental pulmonary arteries; (B) bilateral pulmonary consolidations.

The patient remained hemodynamically stable (Pulmonary Embolism Severity Index 77 points, Class II, low risk); therefore, no indication for a systemic thrombolysis was present. The initial therapy with therapeutic dose of unfractionated heparin (UFH) was switched to an oral anticoagulation with rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily).

The patient could be discharged after 8 intra-hospital days. A control compression ultrasonography of the lower extremities after 6 months showed no signs of thrombosis. The anticoagulation was discontinued and a therapy with acetylsalicylic acid was restarted.

We postulated that DVT in this patient was provoked by initial immobilization due to severe respiratory infection and/or because of enhanced thrombogenicity in COVID-19.

Incidence and Outcomes of SARS-CoV-2-Associated Thrombotic Complications

As the SARS-CoV-2 pandemic progressed, high rates of venous thromboembolism (VTE) in hospitalized patients were observed.¹ Most studies report the incidence of VTE in critically ill patients between 15 and 40%, which is significantly higher compared with other critical illnesses leading to hypercoagulability.² Thrombotic complications occur less commonly in hospitalized noncritically ill patients (2–4%).^{3,4} The risk of VTE persists after inpatient treatment. A 7.2% incidence of VTE in 90 days after admission was reported.⁵ Another study reported a median of 21 days for development of VTE since the onset of COVID-19 disease.⁶

Numbers are not unanimous, but it is commonly reported that PE occurs more frequently than DVT^{1,7,8} and usually independently of DVT, suggesting that thrombosis in pulmonary vasculature is often not a result of embolism from lower extremities but a local process of pulmonary vasculature (microangiopathy vs. macroangiopathy). This is supported by imaging studies which report that pulmonary thromboses are rather found in segmental or subsegmental, that is, smaller and peripheral arteries.^{2,9} Autopsy findings of the lungs of COVID-19 patients also show a significant endothelial damage and microthrombi in alveolar capillaries.¹⁰

Thrombotic complications in COVID-19 disease are associated with worse clinical outcomes. A 24.5% higher all-cause mortality was reported in patients with COVID-19 disease as well as both venous and arterial thrombotic complications.⁴ A recent meta-analysis reports 74% higher odds of death in COVID-19 patients with thrombotic complications.¹¹ During a 90-day follow-up, mortality of 24% was reported; 20.5% deaths were caused by pulmonary embolism (PE) compared with 62.5% due to respiratory failure.¹²

An overview of prevalence of thromboembolism and bleeding complications in COVID-19 disease reported in this review article is presented in [Table 1](#).

Thrombotic Events after Vaccination against SARS-CoV-2

A concern was raised after thrombotic events around the world occurred approximately 14 days after vaccination against SARS-CoV-2 with ChAdOx1 nCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India) vaccine. Seven cases of blood clotting in multiple vessels and 18 cases of cerebral venous sinus thrombosis, which occurred mostly in women under 55 years, were reported.¹³ The first clinical trial on efficacy and safety of ChAdOx1 nCoV-19/AZD1222 vaccine, however, reported no thrombotic adverse events.¹⁴ No thrombotic complications were reported among severe or serious adverse events in a clinical trial for BNT162b2 (Pfizer-BioNTech COVID-19 vaccine).¹⁵ DVT occurred in 2 (<0.1%) subjects after vaccination with mRNA-1273 (Moderna COVID-19 vaccine)¹⁶ and in 1 recipient (0.006%) of Gam-COVID-Vac (Sputnik V) vaccine.¹⁷ More thrombotic events (0.06%) were observed among recipients of Ad26.COV2.S (Janssen COVID-19 vaccine): six cases of DVT, four cases of PE, and three cerebrovascular events, including transverse sinus thrombosis which occurred in a 25-year-old male.¹⁸

Later a similar prothrombotic syndrome to that associated with AstraZeneca COVID-19 vaccine was observed in a small number of patients who received the Janssen COVID-19 vaccine.^{19,20} Thrombotic events were accompanied by thrombocytopenia,²¹ therefore, an entity of vaccine-induced immune thrombotic thrombocytopenia (VITT) has been established.²²

According to the latest findings, VITT is caused by antibodies against platelet factor 4 (PF4), bound to platelets.^{20,23} PF4 causes platelet activation and enhanced thrombosis, on the contrary to other thrombocytopenic disorders.²² The clinical constellation resembles heparin-induced thrombocytopenia (HIT); however, VITT occurs without exposure to heparin.^{20,22,24} Laboratory findings include elevated level of D-dimer, thrombocytopenia, and PF4 antibodies.²¹ It is postulated that production of antibodies against PF4 may be the result of a strong immune response after vaccination or a cross-reaction between vaccine components and platelets/PF4.²²

To this day, benefits of the COVID-19 vaccine outweigh the risk of adverse events; therefore, vaccination with

Table 1 Prevalence of thromboembolism and bleeding complications in COVID-19 disease

Author	Total cohort	VTE	PE	DVT	Bleeding	
					Prophylactic anticoagulation	Therapeutic anticoagulation
Helms et al ¹	n = 179 (ICU)	n = 57, 31.8%	n = 25, 14.0%	n = 11, 6.1%	n = 2	n = 1
Piazza et al ³	n = 1,114 (ICU, non-ICU, outpatient)	n = 51, 4.6%	n = 8, 0.7%	n = 39, 3.5%	-	-
Bilaloglu et al ⁴	n = 3,334 (ICU, non-ICU)	n = 533, 16.0% ^a	n = 106, 3.2%	n = 129, 3.9%	-	-
Al-Samkari et al ⁶⁴	n = 3,239 (ICU)	n = 204, 6.3%	n = 32, 15.7%	n = 176, 86.3%	n = 90, 2.8%	-
Musoke et al ⁶³	n = 355 (ICU, non-ICU)	-	-	-	n = 7, 4.0%	n = 11, 11.0%
Rentsch et al ⁶²	n = 4,297 (ICU, non-ICU)	-	-	-	n = 198, 4.6%	-
Salisbury et al ⁵	n = 303 (ICU, non-ICU)	n = 18, 5.9%	n = 13 (concomitant DVT, n = 3)	n = 5	n = 5	n = 6
Klok et al ⁸	n = 184 (ICU)	27.0%	n = 25, 81.0%	n = 1	-	-
Cohen et al ²⁵	n = 9,407 (ICU, non-ICU)	n = 274, 2.9%	n = 85, 31.0% (concomitant DVT, n = 19)	n = 170, 62.0%	-	-
Fauvel et al ⁶⁶	n = 1,240 (ICU, non-ICU)	-	n = 103, 8.3%	n = 18, 1.5%	-	-

Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.
^aAny thrombotic event.

AstraZeneca COVID-19 vaccine continues. However, further accumulation of evidence to improve diagnosis, management, and prevention of VITT is needed.

Predictors of COVID-19-Associated Venous Thromboembolism

Advanced age (>60 years), male sex, Hispanic ethnicity, and obesity (Body mass index > 35) were found to be risk factors for VTE in COVID-19 disease.^{4,25} Patients with a history of heart failure, cerebrovascular disease, and active malignant disease were more likely to develop VTE.^{6,25} Elevated levels of D-dimers at admission or a fourfold elevation in the course of disease was also associated with risk of VTE and increased mortality.^{6,25}

Occurrence of PE was associated with male sex, history of stroke or atrial fibrillation, and elevated levels of D-dimer and CRP.²⁶ However, after a multivariate analysis, male sex, elevated CRP and time from symptom onset to hospitalization remained significant risk factors for PE.²⁶ Therefore, immunothrombosis seems to be the crucial pathophysiological mechanism in the development of PE in COVID-19 disease, not always driven by typical risk factors for VTE.

Pathophysiology of Enhanced Thrombogenicity in COVID-19 Disease

Reduced blood flow, endothelial damage, and hypercoagulability, also referred to as the Virchow's triad, are the main three factors leading to increased thromboembolism.²⁷

Endothelial damage seems to be one of the key mechanisms in thrombosis in COVID-19 due to disruption of anticoagulant and/or anti-aggregatory function of endothelial cells. SARS-CoV-2 may enter the endothelial cells directly leading to their damage and activation.²⁸ Damaging the endothelium leads to uncovering of the thrombogenic basement membrane and expression of the tissue factor. The latter activates the factors VII and X, which trigger the extrinsic coagulation pathway.

Endothelial cells are also a target of cytokines, e.g., interleukin-1 (IL-1), tumor necrosis factor α , which activate the endothelium enhancing its prothrombotic effects.²⁹ This leads to attraction of leukocytes and chemokines, which then migrate into subendothelial space.²⁹ Dead or dying neutrophils form neutrophil extracellular traps enhancing thrombus formation.³⁰ Endothelial cell activation also causes excretion of von Willebrand factor (VWF), stored in the platelets,³¹ as well as production of prothrombotic thromboxane. Activated platelet degranulation products (e.g., VWF, P-selectin) contribute to platelet aggregation and thrombus formation. Activated platelets also recruit immune cells, cytokines, and interact directly with pathogens, facilitating the coordination of inflammatory and prothrombotic processes.^{32,33} Platelet-monocyte aggregate formation, which triggers tissue factor expression and platelet activation, was observed.³⁴ Recent observations also suggest that platelet gene expression is altered in COVID-19 leading to platelet hyperreactivity.³⁵ In addition,

enhanced megakaryopoiesis with presence of megakaryocytes in pulmonary and cardiac tissues from autopsies of COVID-19 patients has been reported.³⁶ These observations usually occurred without reactive thrombocytosis. Instead, thrombocytopenia has been described as a predictor of poor outcome in COVID-19 patients.³⁷

It remains to be determined whether platelet hyperactivity is specifically linked to SARS-CoV-2 infection or just a reactive response to severe infection comparable to other inflammatory conditions. The prognostic role of antiplatelet therapy apart from other indications for secondary prevention is still unclear and should be carefully weighed against the bleeding risk.

Induced production and activity of plasminogen activator inhibitor-1 (PAI-1) leads to disruption of fibrinolysis, also described as “fibrinolysis shutdown.”^{29,38} Hepatic acute phase response also leads to enhanced production of PAI-1 and fibrinogen causing prothrombotic and fibrinolytic imbalance (→Fig. 2).²⁹ Another acute phase reactant is the coagulation factor VIII which is induced through IL-6 and binds to the nuclear factor-κB of the endothelial cells, further triggering the proinflammatory pathway and enhancing the cytokine storm.^{39,40} The role of these prothrombotic factors is supported by the fact that elevated levels of fibrinogen, factor VIII, and VWF could be detected in plasma of patients with COVID-19 disease.⁴¹

Antiphospholipid antibodies, which can prolong the activated partial thromboplastin time (aPTT), could also be detected in three critically ill patients with SARS-CoV-2 infection⁴²; however, this remains a rare finding so far.

In summary, thrombosis in COVID-19 disease seems to be a complex interplay between the endothelium and a range of proinflammatory cytokines. Moreover, endothelium-based thrombosis is not limited to pulmonary vasculature and rather spreads to cerebral, coronary circulation as well as to venous vasculature.²⁹

Elevated D-dimer in COVID-19 disease seems to be not only a diagnostic tool for thrombosis but also a prognostic marker. Several studies showed a significant relationship between the concentration of D-dimer and the severity of the SARS-CoV-2 infection.⁴³ Plasma D-dimer concentration of

>1 µg/L was a strong predictor of mortality due to COVID-19 disease.⁴⁴

Another cornerstone of thrombosis is hypercoagulability, which is enhanced not only through elevated levels of prothrombotic factors and cytokines as well as hyperviscosity detected by thromboelastography measurements in COVID-19 patients.^{38,41}

Immobilization, especially in hospitalized patients, as a constituent of the Virchow’s triad, also contributes to DVT in COVID-19 disease. However, it seems to be of secondary importance compared with immunothrombosis.

Diagnostics of VTE in COVID-19 Disease

Complete blood count including platelet count, aPTT, and levels of fibrinogen and D-dimer are recommended for routine screening in COVID-19 patients. Prevention or treatment of VTE, however, should not be initiated based on abnormal findings of these laboratory parameters (elevated D-dimer, fibrinogen, prolonged aPTT, or thrombocytopenia/thrombocytosis), if no clinical signs or positive diagnostic findings are present. Abnormal or rapidly rising levels of D-dimer do not confirm the diagnosis of VTE, and adequate diagnostics should be sought, whereas a negative value of D-dimer excludes VTE with high probability if the pretest probability (e.g., Wells score) is low.

Increased D-dimer and thrombocytopenia may raise the suspicion of disseminated intravascular coagulation (DIC) syndrome.⁴⁵ However, levels of clotting factors are usually elevated in COVID-19 patients, contradicting to the consumption of coagulation factors seen in DIC.⁴¹ Furthermore, as already mentioned, thrombotic rather than bleeding complications occur in SARS-CoV-2-infected patients.

A diagnostic approach of PE should include standard imaging tools, e.g., CTPA, and less commonly ventilation/perfusion scan or magnetic resonance imaging, if clinical suspicion arises. Transthoracic echocardiography should also be performed to evaluate right ventricular and tricuspid valve function, pulmonary artery pressures, or detect a thrombus in transit in pulmonary arteries. Compression ultrasonography should be used to detect DVT. If the standard diagnostic tools are not available, a point-of-care compression ultrasonography or echocardiography should be applied. However, bedside imaging may be difficult due to patient instability, prone positioning, etc.⁴⁶

Prevention and Treatment of VTE in COVID-19 Disease

Inpatient Prophylaxis of VTE

Prophylactic anticoagulation reduces the risk of VTE in critically ill COVID-19 patients.⁴⁷ Evidence from randomized trials considering management of VTE in COVID-19 disease is still lacking. Therefore, prevention of VTE in COVID-19 patients should be based on available interim recommendations as well as guidelines on prevention of VTE for general population, e.g., American Society of Hematology,⁴⁸ American College of Chest Physicians,⁴⁹ or National Institute for

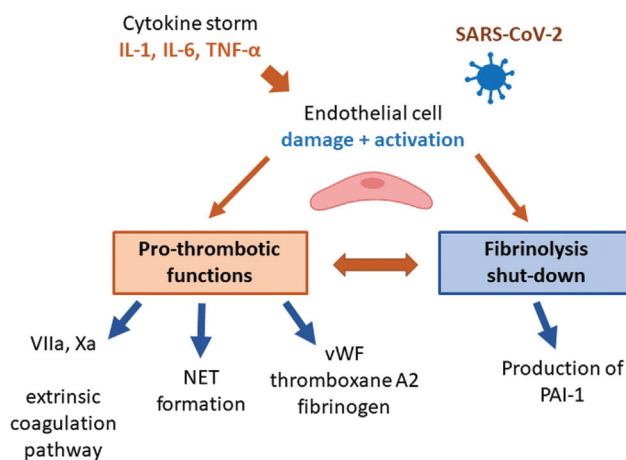


Fig. 2 The pathomechanism of hypercoagulability in COVID-19 disease.

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Health and Clinical Excellence guidelines. Assessment of the risk of VTE in COVID-19 patients can be objectified using extensively validated risk assessment models, e.g., IMPROVE or Padua scores.^{50,51}

Prophylactic-dose anticoagulation is recommended for all hospitalized critically and noncritically ill COVID-19 patients provided no contraindications exist, e.g., bleeding complications, HIT, etc. In general, subcutaneous use of low-molecular-weight heparin (LMWH) once daily, e.g., enoxaparin, dalteparin, tinzaparin, or UFH twice daily, is recommended. Dose adjustment of LMWH based on creatinine clearance or use of UFH is recommended in patients with impaired renal function.⁵²

Mechanical prophylactic measures, e.g., intermittent pneumatic compression, in intensive care unit patients should also be considered when pharmacological prophylaxis is contraindicated.⁵³ Mechanical thromboprophylaxis should not, however, be combined with pharmacological treatment due to lack of evidence.⁴⁶

In some patients, intensified regimens of prophylactic anticoagulation may be considered, as occurrence of VTE despite prophylactic-dose anticoagulation was observed.⁴ In these patients, intermediate dosing of LMWH (twice-daily or increased weight-based dosing) may be chosen.⁴⁶ Several studies report better clinical outcomes (shorter in-hospital stay, reduced mortality) in critically ill COVID-19 patients who received therapeutic anticoagulation without confirmed VTE.^{54,55} The benefit, however, could only be observed in selected patients with certain risk factors for VTE. A multiplatform randomized clinical trial (REMAP-CAP, ACTIV-4, ATTACC) is currently assessing the benefits of full-dose prophylactic anticoagulation in over 1,000 critically ill patients. The occurrence of VTE could be reduced; however, no improvement in survival and no significant reduction of days free of organ support could be observed.⁵⁶ The trial is further investigating the benefit–risk balance of therapeutic anticoagulation in noncritically ill COVID-19 patients.

To this day, empiric therapeutic anticoagulation remains controversial and further accumulation of evidence is needed, but it may be considered when there is a high clinical probability of VTE and no confirmatory imaging is possible, or by clotting of intravascular devices.

Outpatient Prophylaxis of VTE

The risk of VTE may persist in some discharged COVID-19 patients; however, it does not seem to be higher compared with the general population of critically ill patients.⁵⁷ According to current guidelines, it is generally not advisable to extend thromboprophylaxis in critically ill patients postdischarge.^{48,58} The evidence on postdischarge thromboprophylaxis in COVID-19 patients is still lacking. Several ongoing trials are investigating the benefits of extended thromboprophylaxis (apixaban 2.5 mg twice daily [NCT04650087] or rivaroxaban 10 mg once daily [NCT04662684] for approximately 30 days postdischarge), and its influence on occurrence of venous/arterial thromboembolism and/or all-cause mortality.

Currently, extended thromboprophylaxis after discharge in patients with COVID-19 may be considered in patients with high thrombotic risk, e.g., advanced age, cancer, prior history of VTE, known thrombophilia, severe immobility, elevated D-dimer, IMPROVE VTE score of 4 or more, and low bleeding risk, all of which should be evaluated on a case-by-case basis.^{53,59} LMWH or a direct oral anticoagulant for approximately 14 days at least, up to 30 days, may be prescribed.⁵³

In- and Outpatient Treatment of VTE

In case of confirmed VTE in hospitalized COVID-19 patients, therapeutic anticoagulation with weight-adjusted LMWH or UFH should be initiated, according to general guidelines on the treatment of VTE.^{49,60} In patients with high or intermediate clinical probability of VTE, treatment should be initiated before the diagnosis is confirmed by imaging tools.⁶⁰ In patients with VTE and no contraindications (severe renal impairment, pregnancy, antiphospholipid syndrome), DOACs should be chosen over vitamin K antagonists (VKAs).^{49,60} Patients with VTE and cancer should be treated with LMWH or rivaroxaban, apixaban if no gastrointestinal cancer is present.⁶⁰ DOACs are not recommended as initial therapy due to possible drug-to-drug interactions or in case of deteriorating hemodynamic and/or respiratory situation of the patient.⁵³ Therapeutic anticoagulation in discharged patients should be continued with a DOAC or VKA for at least 3 months based on the guidelines of management of VTE in general population; the bleeding risk should be evaluated individually.^{49,60}

Bleeding Complications Associated with Therapeutic/Prophylactic Anticoagulation

Evidence on the benefits of anticoagulation in COVID-19 disease to this day is rather inconsistent. Diminishing micro- and/or macrothrombosis with prophylactic or therapeutic anticoagulation results in reduced all-cause mortality, as long as no significant increase in bleeding complications is observed.^{54,55,61,62} On the contrary, several studies report on increased mortality in patients receiving anticoagulation, mainly due to adverse bleeding events.^{63,64} Incidence of bleeding complications in COVID-19 disease is reported to be around 1.7 to 4.6% under prophylactic and 2.8 to 11% under full-dose anticoagulation (–Table 1).^{61,64}

Discrepancies in reported data may arise as outcomes are compared in different patient cohorts (consecutive SARS-CoV-2 positive vs. only critically ill patients), definition of bleeding varies, differences between types and dosage of anticoagulants exist, etc.

Finally, anticoagulation may not be the only therapeutic approach in VTE, as thrombosis in SARS-CoV-2 infection is partly a result of a cytokine storm; therefore, control of inflammatory response may also be crucial.

Summary

SARS-CoV-2 infection is associated with increased risk of VTE compared with other critical illnesses. Reported incidence of

VTE ranges from 15 to 40%. Thrombotic complications accompanying COVID-19 disease are associated with significantly increased mortality. Several pathophysiological mechanisms leading to enhanced thrombogenicity in SARS-CoV-2 infection have been identified so far. Endothelial cell damage and excessive inflammatory response lead to activation and enhanced prothrombotic functions of the endothelium. Simultaneously, inhibition of fibrinolysis results in a prothrombotic and fibrinolytic imbalance and enhanced thrombus formation. Prophylactic-dose anticoagulation is recommended for all hospitalized COVID-19 patients and should be extended after discharge. The benefit of a full-dose anticoagulation for thromboprophylaxis remains controversial. Confirmed VTE is treated with therapeutic anticoagulation according to the guidelines on management of VTE in general population. Immunothrombosis is a crucial aspect of COVID-19 disease and further evidence on optimal management of VTE needs to be accumulated.

Zusammenfassung

COVID-19 geht mit erhöhtem Risiko thromboembolischer Komplikationen gegenüber zu anderen mit akutem Atemnotsyndrom assoziierten Infektionserkrankungen einher. Die Inzidenz von venösen Thrombosen variiert zwischen 15 bis 40%. Thromboembolische Komplikationen im Rahmen einer COVID-19 Erkrankung sind mit erhöhter Mortalität assoziiert. Einige pathophysiologische Mechanismen erhöhter Thrombogenität in SARS-CoV-2 Infektion konnten bereits identifiziert werden. Endothelschaden und übermäßige Inflammation triggern prothrombotische Endothelfunktionen. Störungen in fibrinolytischen Prozessen resultieren in einem Missverhältnis zwischen Thrombose und Fibrinolyse und somit gesteigerter Thrombusbildung. Eine Thromboseprophylaxe wird für alle stationären Patienten empfohlen und sollte im ambulanten Bereich fortgesetzt werden. Der Nutzen therapeutischer Antikoagulation zur Thromboseprophylaxe verbleibt umstritten. Bestätigte venöse Thromboembolien sollten entsprechend den vorhandenen Leitlinien behandelt werden. Da die Immunthrombose einen wichtigen Aspekt im Rahmen einer COVID-19 Erkrankung darstellt, sind weitere Untersuchungen zur optimalen Therapie venöser Thromboembolien notwendig.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

- 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;46(06):1089–1098
- Waite AAC, Hamilton DO, Pizzi R, Ageno W, Welters ID. Hypercoagulopathy in severe COVID-19: implications for acute care. *Thromb Haemost* 2020;120(12):1654–1667
- Piazza G, Campia U, Hurwitz S, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. *J Am Coll Cardiol* 2020;76(18):2060–2072
- Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. *JAMA* 2020;324(08):799–801
- Salisbury R, Iotchkova V, Jaafar S, et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. *Blood Adv* 2020;4(24):6230–6239
- Li J-Y, Wang H-F, Yin P, et al; Thrombo-COVID-19 Collaborative. Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: a multicenter retrospective study. *J Thromb Haemost* 2021;19(04):1038–1048
- Porfida A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thromb Res* 2020;196:67–74
- 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
- Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020;173(05):350–361
- Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020;173(04):268–277
- Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:100639
- Demelo-Rodríguez P, Ordieres-Ortega L, Ji Z, et al. Long-term follow-up of patients with venous thromboembolism and COVID-19: analysis of risk factors for death and major bleeding. *Eur J Haematol* 2021;106(05):716–723
- EMA. COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. Accessed March 18, 2021 at: <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>
- Folegatti PM, Ewer KJ, Aley PK, et al; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;396(10249):467–478
- Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383(27):2603–2615
- Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(05):403–416
- Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397(10275):671–681
- FDA. Briefing Document FDA. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19 Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021. Accessed February 24, 2021 at: <https://www.fda.gov/media/146217/download>

- 19 Aleem A, Nadeem AJ. Coronavirus (COVID-19) vaccine-induced immune thrombotic thrombocytopenia (VITT). In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021
- 20 Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021;384(22):2124–2130
- 21 Favaloro EJ. Laboratory testing for suspected COVID-19 vaccine-induced (immune) thrombotic thrombocytopenia. *Int J Lab Hematol* 2021;43(04):559–570
- 22 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021;384(22):2092–2101
- 23 Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021;384(23):2202–2211
- 24 Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT): diagnostic and therapeutic recommendations for a new syndrome. *Eur J Haematol* 2021;107(02):173–180
- 25 Cohen SL, Gianos E, Barish MA, et al; Northwell Health COVID-19 Research Consortium. Prevalence and predictors of venous thromboembolism or mortality in hospitalized COVID-19 patients. *Thromb Haemost* 2021;121(08):1043–1053
- 26 Fauvel C, Weizman O, Trimaille A, et al; Critical Covid-19 France Investigators. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020;41(32):3058–3068
- 27 Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol* 2008;143(02):180–190
- 28 Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383(02):120–128
- 29 Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J* 2020;41(32):3038–3044
- 30 Middleton EA, He X-Y, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood* 2020;136(10):1169–1179
- 31 O'Sullivan JM, Gonagle DM, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. *Lancet Haematol* 2020;7(08):e553–e555
- 32 Colling ME, Kanthi Y. COVID-19-associated coagulopathy: an exploration of mechanisms. *Vasc Med* 2020;25(05):471–478
- 33 Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. *Pathobiology* 2021;88(01):15–27
- 34 Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood* 2020;136(11):1330–1341
- 35 Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. *Blood* 2020;136(11):1317–1329
- 36 Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. *EClinicalMedicine* 2020;24:100434
- 37 Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. *J Thromb Haemost* 2020;18(06):1469–1472
- 38 Hammer S, Häberle H, Schlensak C, et al. Severe SARS-CoV-2 infection inhibits fibrinolysis leading to changes in viscoelastic properties of blood clot: a descriptive study of fibrinolysis in COVID-19. *Thromb Haemost* 2021;121:1417–1426. doi: 10.1055/a-1400-6034
- 39 Begbie M, Notley C, Tinlin S, Sawyer L, Lillicrap D. The factor VIII acute phase response requires the participation of NFkappaB and C/EBP. *Thromb Haemost* 2000;84(02):216–222
- 40 Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol* 2009;1(06):a001651
- 41 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 Thromb Haemost* 2020;18(07):1738–1742
- 42 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
- 43 Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. *Expert Rev Hematol* 2020;13(11):1265–1275
- 44 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
- 45 Levi M, Toh CH, Thachil J, Watson HGBritish Committee for Standards in Haematology. Guidelines for the diagnosis and management of disseminated intravascular coagulation. *Br J Haematol* 2009;145(01):24–33
- 46 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;158(03):1143–1163
- 47 Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020;75(23):2950–2973
- 48 Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018;2(22):3198–3225
- 49 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149(02):315–352
- 50 Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010;8(11):2450–2457
- 51 Spyropoulos AC, Anderson FAJ Jr, FitzGerald G, et al; IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest* 2011;140(03):706–714
- 52 Piazza G, Morrow DA. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. *JAMA* 2020;324(24):2548–2549
- 53 Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. 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(08):1859–1865
- 54 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 Thromb Haemost* 2020;18(05):1094–1099
- 55 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(01):122–124
- 56 Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic anticoagulation with Heparin in critically ill patients with Covid-19. *N Engl J Med* 2021;385(09):777–789. Doi: 10.1056/NEJMoa2103417

- 57 Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood* 2020;136(11):1347–1350
- 58 Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e195S–e226S
- 59 Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020;50(01):72–81
- 60 Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41(04):543–603
- 61 Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020;76(16):1815–1826
- 62 Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ* 2021;372(311):n311
- 63 Musoke N, Lo KB, Albano J, et al. Anticoagulation and bleeding risk in patients with COVID-19. *Thromb Res* 2020;196:227–230
- 64 Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020;136(04):489–500