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.

Keywords
► SARS-CoV-2
► COVID-19
► thrombosis
► venous thromboembolism

Zusammenfassung
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. A recent meta-analysis reports 74% higher odds of death in COVID-19 patients with thrombotic complications. 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.

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. The first clinical trial on efficacy and safety of ChAdOx1 nCoV-19/AZD1222 vaccine, however, reported no thrombotic adverse events. No thrombotic complications were reported among severe or serious adverse events in a clinical trial for BNT162b2 (Pfizer-BioNTech COVID-19 vaccine). DVT occurred in 2 (<0.1%) subjects after vaccination with mRNA-1273 (Moderna COVID-19 vaccine) and in 1 recipient (0.006%) of Gam-COVID-Vac (Sputnik V) vaccine. 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.

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. Thrombotic events were accompanied by thrombocytopenia, therefore, an entity of vaccine-induced immune thrombotic thrombocytopenia (VITT) has been established.

According to the latest findings, VITT is caused by antibodies against platelet factor 4 (PF4), bound to platelets. PF4 causes platelet activation and enhanced thrombosis, on the contrary to other thrombocytopenic disorders. The clinical constellation resembles heparin-induced thrombocytopenia (HIT); however, VITT occurs without exposure to heparin. Laboratory findings include elevated level of D-dimer, thrombocytopenia, and PF4 antibodies. 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.

To this day, benefits of the COVID-19 vaccine outweigh the risk of adverse events; therefore, vaccination with...
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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, 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 antiplaquette 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
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.56

In some patients, intensified regimens of prophylactic anticoagulation may be considered, as occurrence of VTE despite prophylactic-dose anticoagulation was observed.54 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.49,50 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 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

Conflict of Interest
The authors declare that they have no conflict of interest.

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