Chapter 12
Thromboembolic Events in COVID-19

Maria Wieteska-Miłek and Marcin Kurzyna

Abbreviations

ASA	Acetylsalicylic acid
ATE	Arterial thromboembolism
COVID-19	Coronavirus disease 2019
CTPA	CT pulmonary angiography
DVT	Deep venous thrombosis
HFU	Unfractionated heparin
ICU	Intensive care unit
LMWH	Low-molecular-weight heparin
PE	Pulmonary embolism
VTE	Venous thromboembolism
VUS	Venous ultrasound

Patients with coronavirus disease 2019 (COVID-19) are exposed to an increased risk for thromboembolic complications. Thromboembolic events that frequently occur in COVID-19 are most often located in the lungs and are more common in severe COVID-19; thromboembolic events are also associated with significantly higher mortality rates in patients with severe COVID-19 [1–3]. Macroscopic thrombus formation or in situ thrombosis in the branches of pulmonary arteries are found in 60% of deceased COVID-19 patients [4]. Apart from significant generalized pulmonary tissue oedema, autopsy examinations reveal massive inflammatory

M. Wieteska-Miłek · M. Kurzyna (✉)
Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Center of Postgraduate Medical Education, European Health Center, Otwock, Poland
e-mail: maria.wieteska@ecz-otwock.pl; marcin.kurzyna@ecz-otwock.pl

M. Banach (ed.), *Cardiovascular Complications of COVID-19*, Contemporary Cardiology, https://doi.org/10.1007/978-3-031-15478-2_12

infiltration of leukocytes within endothelial cells (mainly neutrophils) and microthrombosis in pulmonary capillaries, including alveolar septal capillaries [5]. Thrombotic events can also affect medium-sized vessels, leading to pulmonary infarction [5]. The pathogenesis of thromboembolism in COVID-19 is not fully understood, but it is known to involve hypoxemia, excessive inflammatory response, endothelial cell damage, impaired blood flow, and platelet activation. Thromboembolism is common in hospitalized patients, especially in critically ill patients. The prevention and optimal treatment of thromboembolic episodes is still a matter of debate and research. This chapter discusses the main aspects of epidemiology and risk factors, pathophysiological mechanisms, diagnosis, and management of thromboembolic events in COVID-19 patients.

Epidemiology

Thromboembolism in patients with COVID-19 most often manifests as venous thromboembolism (VTE), such as pulmonary embolism (PE) and/or deep vein thrombosis (DVT), and less often by arterial thromboembolism (ATE). An increased risk of blood clots in COVID-19 patients is well documented. An increased incidence of thromboembolic events in COVID-19 patients was first reported as early as at the beginning of the COVID-19 outbreak.

Klok et al. reported that 31% of 184 patients in intensive care unit (ICU) with proven pneumonia secondary to COVID-19 who received usual-care thromboprophylaxis experienced thromboembolic events, including VTE confirmed by computed tomography pulmonary angiography (CTPA) and/or ultrasonography of the lower extremity veins (VUS) (27% of patients), and arterial thromboembolism (3.7% of patients) [2]. In another single center observational study by Lodigiani et al. on a group of 388 patients with COVID-19 infection, including 17% of ICU patients, as many as 21% of ICU patients had VTE despite thromboprophylaxis, and half of the VTE cases were diagnosed within the first 24 h of hospitalization. Overall, VTE occurred in 4.4%, ischemic stroke in 2.2%, myocardial infarction in 1.1% of these patients [6]. In an observational study by Middeldorp et al. of 199 COVID-19 patients, including 38% of ICU patients, 47% of ICU patients developed VTE despite standard thromboprophylaxis, of which 16% within the first 7 days of admission [3].

The frequency of VTE in patients with COVID-19 varies considerably. In 15 observational studies carried out worldwide, the frequency of VTE was 0.9–69% (6.7–69% in ICU patients and 0.9–6.5% in non-ICU patients) [7]. The incidence of VTE was significantly higher than that of ATE (2.7–3.8%) [7]. PE in ICU patients occurred in 16.7% to 35% of critically ill COVID-19 patients, DVT—in 0.5% to 69% of ICU patients, and in 0% to 46.1% of non-ICU patients [7]. The difference in the incidence rates of VTE, PE, and DVT can be attributed to the various diagnostic strategies and algorithms used across hospital departments. In another meta-analysis by Porfidia et al. based on observational studies of 3487 patients hospitalized for

COVID-19 in 30 sites, the risk of VTE was estimated at 26%. PE with or without DVT was diagnosed in 12% of patients, and DVT alone in 14% of patients. In sites that used a standard diagnostic algorithm to confirm VTE, PE was diagnosed in 13% of patients and DVT in 6% of patients. As for sites that used a diagnostic algorithm other than the standard one, PE was diagnosed in 11%, and DVT in 24% of patients [8]. There was also a large difference in the incidence of VTE between hospitalized ICU and non-ICU patients. VTE was diagnosed in 24%, PE in 19%, and DVT alone in 7% of patients receiving ICU care. The incidence of PE was much lower among hospitalized non-ICU patients—9% for VTE in total, 4% for PE, and 7% for DVT [8]. In another meta-analysis of 48 studies by Jimenez et al., the total incidence of VTE was estimated at 17.3% of hospitalized COVID-19 patients, of which two-thirds had DVT and one-third had PE [9]. Distal DVT, catheter-related thrombosis associated with the use of a central venous catheter, or subsegmental PE were diagnosed in a significant proportion of these patients, which may be associated with a local inflammatory response to COVID-19 [9].

These observations are consistent with the data collected in a multicenter observational study by Japanese investigators on a group of 1236 COVID-19 patients—VTE was diagnosed in 22.2% of these patients. The overall incidence rates of VTE varied depending on the severity of COVID-19: 40% with severe COVID-19 (patients who required mechanical ventilation), 11.8% with moderate COVID-19 (patients who required oxygen therapy), and 0% with mild COVID-19 (patients who did not require oxygen therapy) [10].

Pathogenesis

The pathogenesis of thromboembolic complications in patients with COVID-19 is complex and multifactorial [11]. The frequency of VTE in COVID-19 is higher than in other viral diseases, such as infections with H1N1 influenza or SARS-CoV-1, which suggests the involvement of other pathogenetic mechanisms of VTE, although the different research methods used can make such comparison difficult [11–13].. VTE is also much more prevalent in COVID-19 than in acute respiratory distress syndrome (ARDS), which indicates that other additional mechanisms can contribute to the increased risk of VTE, in addition to severe and acute respiratory insufficiency and immobilization [14]. In post-mortem studies of patients who died of acute respiratory failure in the course of COVID-19 infection, diffuse alveolar damage with hyaline membrane formation and atypical type II pneumocyte hyperplasia were predominant in histopathological examinations. Most lung autopsies (33/38) reported platelet–fibrin thrombi in the small pulmonary vasculature [15].

Blood clots in small pulmonary vessels may result from in situ immune-mediated thrombosis and/or classic VTE, or both [11]. Coagulopathy typical of COVID-19 includes mild thrombocytopenia, slightly prolonged prothrombin time, and elevation of fibrinogen and D-dimer [11, 16]. These abnormalities are not specific for COVID-19 as they also occur in sepsis-induced coagulopathy (SIC) and in

disseminated intravascular coagulation (DIC) [17]. The activity of von Willebrand factor (vWf) is typically increased. There is also an increase in inflammatory markers: ferritin, C-reactive protein, procalcitonin, and leukocytosis. Lymphopenia and neutrophilia have been reported [11]. Typically, the levels of antithrombin, protein C/S, and alpha-antiplasmin-endogenous anticoagulants in COVID-19 infection are normal, which distinguishes COVID-19-associated coagulopathy from DIC [18]. Damage to the vascular endothelium induced by the virus and the resulting endothelial dysfunction is an important feature in the pathogenesis of COVID-19-associated thromboembolism. A healthy endothelium provides immune and barrier functions and is also responsible for regulating vascular tone. Activation of endothelial cells and reduction of endothelium-dependent vasodilation promote the development of inflammation and thrombosis [11]. Also, the synthesis of nitric oxide and prostacyclin was found to be impaired in patients with COVID-19 [19]. The vascular tone is also mediated by the local renin angiotensin aldosterone system (RAAS). ACE2 enzyme produces Ang-(1–7) from angiotensin II (AngII), which prevents the accumulation of Angiotensin II to protect the body against excessive vasoconstriction. The SARS-CoV-2 virus suppresses the ACE2 receptor by internalization and inhibits its activity, which causes secondary accumulation of AngII and excessive vasoconstriction mediated by AngII, and the activation of TF and PAI-1 expression on platelets, which promotes intravascular coagulation and pulmonary tissue damage, and can contribute to thromboembolic events [11, 20]. The ACE2/AngII imbalance may be associated with an increased risk of severe COVID-19 and thromboembolic events among patients with diabetes, heart failure, and arterial hypertension [11]. It is not entirely clear whether ACE2 is present in endothelial cells, however, it was confirmed to be present in pericytes (undifferentiated mesenchymal stem cells that encompass blood vessels and surround endothelial cells) [21]..

COVID-19 infection can be accompanied by increased coagulation and fibrinolysis impairment. As a result of endothelial cell damage and dysfunction, collagen and the tissue factor present in the subendothelial layer become exposed, an exogenous coagulation process is activated, fibrinogen is converted to fibrin, and a platelet plug is formed. The tissue factor expression is also mediated by pro-inflammatory cytokines on macrophages and platelets [11]. The endogenous system is activated on contact between coagulation factor XII (Hageman's contact factor) and kallikreins, collagen, and kininogens (plasma proteins). This results in the formation of active factor XII and a cascade reaction that leads to the development of clinically important clots. Endothelial cell activation markers such as von Willebrand factor, factor VIII, and P-selectin are elevated in COVID-19 infection. Their presence in patients with COVID-19 is associated with a worse prognosis [18]. Fibrinolysis is impaired in COVID-19 patients. The levels of plasminogen activator inhibitor PAI-1 increase, ultimately leading to impaired fibrin degradation [18].

Blood platelets clearly play an important role in blood clot formation in COVID-19 infection. Unlike DIC, platelet levels are normal or only slightly decreased. However, platelets can be hyper-activated [22]. Elevated levels and activity of the von Willebrand factor were observed in patients with COVID-19, which

promotes the formation of primary platelet plug and stimulates the activation and aggregation of blood platelets [18]. Hypoxia has been reported in moderate to severe COVID-19 infections [11]. Endothelial cell become dysfunctional in response to hypoxia, and hypoxia-induced transcription factors (HIF) are expressed in endothelial cells and immune cells. HIFs promote thrombosis by stimulating the release of PAI-1, pro-inflammatory cytokines TNFα, IL-2, and by reducing thrombomodulin expression [23]. The activation of HIFs can trigger an excessive immune response [11].

COVID-19 infection is associated with impaired regulation of the immune system, which promotes blood clots. Uncontrolled excessive release of pro-inflammatory cytokines has been reported in severe COVID-19. This process, referred to as a "cytokine storm," is believed to be one of the key mechanisms leading to the critical deterioration in COVID-19 and an increased risk of thromboembolic events [24–26]. During COVID-19 infection, the concentration of cytokines and chemokines such as IL-2, IL-6, TNFα, INFν increases, which exacerbates inflammatory and pro-thrombotic reactions [11, 26]. Patients with COVID-19 experience excessive complement activation, mainly associated with the deposition of C5b-9 complex in the lung tissue, which promotes microthrombosis [27].

Higher levels of WBC count are observed in COVID-19 infection. Pulmonary post-mortem findings revealed massive leukocyte infiltration patterns in the lung tissue [5]. Leukocytes promote the growth of thromboembolic lesions. Neutrophils are hyperactivated in patients with COVID-19, which leads to excessive expulsion of neutrophil extracellular traps (NETs). These are not effectively eliminated from the body. The role of NETs is to catch pathogens such as viruses and bacteria, but they can damage the body's own tissues when in excess. This is because proteases in NETs, including neutrophilic elastase, can facilitate viral entry into cells by modifying surface proteins in the viral envelope. In addition, they promote the formation of blood clots and the activation of the complement system [11, 28].

Genetic risk factors can also predispose to VTE. In addition to the known classic types of thrombophilia, such as protein C or S deficiency, antithrombin deficiency, mutation of the prothrombin gene or factor V Leiden, blood groups ABO may also be predisposed to severe COVID-19 and thromboembolic complications [11]. Patients with blood group A were shown to have a higher risk of severe COVID-19, and the blood group O may have a lower risk of severe COVID-19 illness. This is believed to be associated with the fact that individuals with blood group O have significantly lower expression (c. 25%) of vWF, which is necessary platelet activation [29]. In addition, anti-A antibodies can inhibit the interaction of SARS-Cov-2 with the ACE2 receptor [30]. There are also other known risk factors for VTE in COVID-19 patients, such as older age, immobilization, comorbid cancer, heart failure, chronic respiratory failure, obesity, hormone therapy, etc., which increase the risk of VTE [31]. A meta-analysis by Cui et al. identified male gender, obesity, mechanical ventilation, significant lung parenchymal injury, admission to ICU, and elevated D-dimers and white blood cells at two time points, on admission and before CTPA, as the risk factors for PE in patients with COVID-19 [32].

The Diagnosis of VTE in COVID-19

Diagnostic testing for VTE in patients with COVID-19 may be difficult, but is recommended in international guidelines; the diagnostic approach is similar in patients with COVID-19 and in non-COVID-19 individuals. VTE in COVID-19 patients should be suspected in the case of: a rapid increase in hypoxemia, increasing oxygen requirements disproportionate to changes in lung parenchyma, sudden drops in blood pressure unexplained by other reasons, or the worsening of tachycardia.

CTPA remains the key diagnostic examination for VTE in COVID-19 patients (Fig. 12.1). Venous compression test of the lower extremities should be performed when symptoms of deep vein thrombosis in the legs are present. VUS can be a valuable diagnostic examination especially where VTE is suspected and imaging tests may be difficult, in unstable patients, in patients requiring high-flow nasal cannula oxygenation, CPAP or intubation. In this case, the diagnosis of venous thrombosis validates the presence of VTE and drives the initiation of anticoagulant treatment, but a negative result does not exclude VTE [33]. Right ventricle dysfunction and signs of right ventricle pressure overload are common in patients with moderate to severe COVID-19-related ARDS. A transthoracic echocardiogram (TTE) is not a routine diagnostic test for VTE, but is used for risk stratification in pulmonary

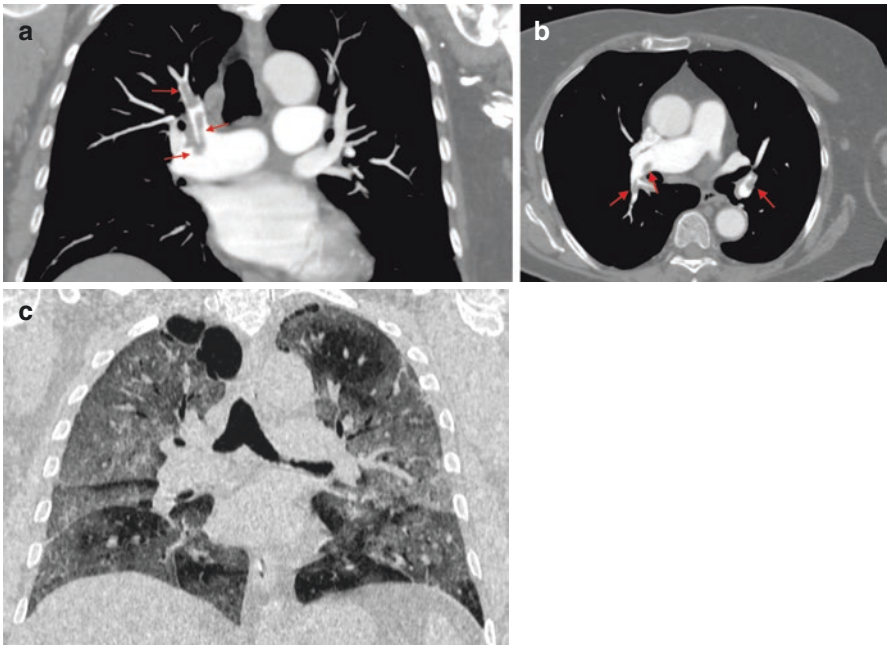

Fig. 12.1 Acute pulmonary embolism in patients with COVID-19 pneumonia. Emboli present in right upper lobe artery (**a**) and intermediate and left lower lobe artery (**b**) at CT pulmonary angiography. Bilateral lung involvement and ground-glass opacities at high-resolution CT lung scan (**c**)

embolism. In some clinical situations, the signs of severe right ventricular dysfunction in an unstable patient or the presence of thrombi in the right heart cavities may warrant anticoagulation or even thrombolytic therapy [34].

D-dimer serves as a valuable marker of activation of the coagulation and fibrinolysis systems [35]. D-dimer is a two-peptide fragment formed from the enzymatic breakdown of cross-linked fibrin. D-dimer is a highly sensitive, yet not very specific marker in the diagnosis of VTE. D-dimer levels are elevated in most patients with SARS-CoV-2 infection [36]. Already in the early stages of the COVID-19 outbreak in Wuhan, almost half of the patients hospitalized for COVID-19 were reported to have elevated levels of D-dimers >500ug/l. Elevations in D-dimers were found in 43% of patients with milder COVID-19 and in 60% of those with severe COVID-19 disease [37]. D-dimer increases in the first day after the infection, and the D-dimer value has been reported to be a valuable predictive and prognostic marker as far as the risk of severe COVID-19 is concerned [38–40]. D-dimer value can be used as a screening test for VTE [41]. COVID-19 patients with VTE events exhibit higher D-dimer levels than COVID-19 patients without VTE [41]. No optimal cut-off point for D-dimer has been established for diagnosing VTE. Mouhat et al. concludes that D-dimer of 2590 μg/L is predictive of pulmonary embolism in patients with COVID-19 with 83% sensitivity and 84% specificity [42]. Three cut-off points for D-dimer and associated risk of VTE were identified in a study of 1739 patients hospitalized for COVID-19. D-dimer <1000 μg/L was associated with a low risk of VTE, D-dimer of 1000–7500 μg/L with an intermediate risk of VTE, and D-dimer >7500 μg/L with a high risk of VTE in patients with COVID-19 [43]. Kwee et al. analyzed 71 studies of patients with COVID-19 with known D-dimer values who also underwent CTPA and proposed a D-dimer value of at least 1000 μg/L as the cut-off point above which CTPA should be carried out to confirm or rule out VTE [44].

Treatment

The management of confirmed new cases of VTE in patients with COVID-19 does not differ from the generally accepted standards of care in VTE [33, 45]. Hospitalized COVID-19 patients with coexisting VTE may benefit more from low-molecular-weight heparin (LMWH) or unfractionated heparin (HFU) than from other anticoagulants due to the lower risk of interactions with antiviral drugs and easier options to reverse the anticoagulant effect in the event of an overdose. Moreover, patients on LMWH do not require additional coagulation monitoring, which means healthcare professionals caring for infected patients are exposed to a lower risk of contracting COVID-19 [33]. Apart from individual case studies, there are no comprehensive studies that examine the thrombolytic therapy for VTE in patients infected with COVID-19, but it should be assumed that the patient management is essentially consistent with the generally accepted standards of care in VTE [33, 45]. Single cases of successful interventional treatment or cardiac surgery in patients with coexisting PE and COVID-19 have also been reported [46, 47].

The duration of anticoagulation treatment following an episode of VTE associated with COVID-19 infection remains controversial. Anticoagulation should last 3 months in moderate to severe COVID-19 infection as a strong reversible risk factor for thromboembolic complications. In VTE associated with mild COVID-19, this risk factor is rather weak and chronic anticoagulation should be continued for a longer period, with regular assessment of the benefit-risk ratio. Long duration of the symptoms of exercise dyspnea, weakness, and fatigue are arguments in favor of extended anticoagulation therapy in COVID-19-associated VTE as these symptoms may indicate persisting lesions in the lung parenchyma or vessels and an increased risk of developing chronic thromboembolic pulmonary disease.

Patients receiving anticoagulants at diagnosis of COVID-19 should continue their treatment and the form of treatment should not be modified, to the extent possible. Except for critically ill patients or patients with artificial heart valves, DOACs are the optimal form of chronic anticoagulation because of the predictable intensity of blood thinning and less frequent treatment monitoring.

Thromboprophylaxis in Patients with COVID-19

Thromboprophylaxis reduces the risk of VTE in hospitalized patients with pneumonia, heart failure, cancer, and in immobilized patients [40]. Antithrombotic prophylaxis should be initiated on admission in all COVID-19 patients, unless it is contraindicated. The doses of antithrombotic prophylaxis have not been yet agreed. In observational studies of patients with COVID-19, a standard dose of low-molecular-weight heparin prophylaxis in all COVID-19 patients was associated with a 21–31% risk of symptomatic VTE [2, 48]. Novel oral anticoagulants or the additional use of acetylsalicylic acid in the context of the pathogenesis of VTE in COVID-19 have also caught the attention of researchers. The differences in international guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 reflect these uncertainties. However, all guidelines highlight the importance of individual decision making according to the assessment of VTE risk factors profile and bleeding risk [33, 49–51] The guidelines of the American Society of Hematology recommend primary antithrombotic prevention at a standard low dose, while the International Society of Thrombosis and Hemostasis recommends higher (intermediate) prophylactic doses for patients at the highest risk (critically ill ICU patients) [51].. Based on recent studies, it has been suggested that therapeutic doses should be considered in hospitalized patients with significantly elevated D-dimers [52, 53]. When the contraindications to pharmacologic thromboprophylaxis exist, mechanical methods should be considered, most preferably graduated compression stockings or intermittent pneumatic pressure.

In a meta-analysis by Jimenez et al. covering 48 studies describing the epidemiology of VTE in hospitalized COVID-19 patients, no significant differences were found in the incidence of VTE depending on the dose of low-molecular-weight heparin used in hospitalized COVID-19 patients [9]. The combined total bleeding

rate was 7.3% [9]. It was the highest in patients on intermediate or high dose LMWH (21.4%), and was significantly higher than in patients receiving standard primary thromboprophylaxis (5%), or in patients who did not receive any prophylaxis (4%) [9]. Major bleeding events occurred in 3.9% of patients [9].

In a multicenter prospective study (The HEP-COVID Randomized Clinical Trial), 557 critically ill patients with severe COVID-19 were randomized. Indications for treatment with therapeutic doses of LMWH were defined as D-dimer levels at least four times the upper limit of normal and a sepsis-induced coagulopathy score (SIC) of 4 or higher. The patients were randomized into two groups—standard thromboprophylaxis or extended LMWH or HFU thromboprophylaxis. The second group received therapeutic-dose LMWH. The therapeutic-dose LMWH was found to reduce the risk of the composite outcome of VTE, ATE, and all-cause mortality in patients hospitalized for COVID-19, but no benefit accrued to patients receiving ICU care [52].

The RAPID study assessed the effectiveness of therapeutic heparin (LMWH or UFH) compared with prophylactic heparin among moderately ill hospitalized patients with COVID-19. The study enrolled 465 hospitalized COVID-19 patients with increased D-dimer levels within 5 days of hospital admission and oxygen saturation ≤93% on room air or D-dimer ≥2 times ULN with normal saturation. Moderately ill patients were defined as patients hospitalized but not requiring mechanical ventilation on admission (non-ICU on admission) [54]. The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or admission to an intensive care unit, assessed up to 28 days of observation. The primary outcome was not achieved in patients assigned to therapeutic heparin, but a reduced mortality rate and low risk of bleeding were observed [54]. Major bleeding occurred in 0.9% of patients assigned to therapeutic heparin and in 1.9% of patients assigned to prophylactic heparin [54].

In a joint open-label randomized trial, REMAP-CAP, ACTIV-4a, and ATTACC investigators assessed whether moderately ill patients hospitalized for COVID-19, i.e., those requiring non-ICU hospitalization, could benefit from additional therapeutic-dose anticoagulation [53]. The study enrolled 2219 patients hospitalized for COVID-19 who were noncritically ill and did not require organ support in an intensive care unit on admission [53]. The patients were randomized to receive either therapeutic-dose anticoagulation or usual-care pharmacologic thromboprophylaxis. The primary outcome was combined in-hospital death and the number of days free of cardiovascular and/or respiratory organ support up to day 21 observation. Of the 1093 patients in the therapeutic-dose anticoagulation group, 94.7% received a LMWH, most commonly enoxaparin. Among the 855 patients in the thromboprophylaxis group, 71.7% received a low dose of a thromboprophylactic drug and 26.5% received an intermediate dose. In the therapeutic-dose anticoagulation group, 82.2% of patients survived until hospital discharge without receipt of organ support during the first 21 days of observation, as compared with 76.4% of patients in the usual-care thromboprophylaxis group. Therapeutic-dose anticoagulation with heparin decreased ICU care and organ support (oxygen delivered by high-flow nasal cannula, NIV/CPAP, mechanical ventilation, or the use of

vasopressors or inotropes) in patients stable at enrollment and these benefits were most pronounced in patients with high levels of D-dimer (≥2 times the upper limit of the normal range [ULN]) [53].

REMAP-CAP, ACTIV-4, and ATTACC investigators also assessed whether the use of therapeutic-dose LMWH in patients requiring ICU could bring additional benefits. A total of 1098 patients were enrolled, 534 assigned to therapeutic-dose anticoagulation and 564 assigned to usual-care thromboprophylaxis. The primary outcome—a composite of organ support-free days and in-hospital death rates evaluated on an appropriate scale, and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge—was not obtained in the therapeutic-dose anticoagulation group [55]. ICU patients did not benefit from more intensive therapeutic-dose anticoagulation, which involves a higher risk of major bleeding. Major bleeding occurred in 3.8% of the patients assigned to therapeutic-dose anticoagulation and in 2.3% of those assigned to usual-care pharmacologic thromboprophylaxis [55].

Another prospective multicenter study with the acronym ACTION assessed the benefits of therapeutic-dose anticoagulation with the use of novel oral anticoagulants compared with prophylactic-dose anticoagulation [45]. Patients receiving therapeutic-dose anticoagulants received rivaroxaban 20 mg or 15 mg 1× daily if diagnosed with renal failure of GFR 30–40 ml/kg/min or concomitantly using azithromycin. If the patient was unstable at baseline, LMWH 1 mg/kg 2× daily or therapeutic dose of HFU was administered. Patients assigned to anticoagulants at prophylactic dose received LMWH or HFU. Patients with confirmed diagnosis of COVID-19 admitted to hospital were enrolled. Inclusion criteria also included D-dimer above the upper limit of normal [45]. Both stable non-ICU and unstable ICU patients were enrolled in the study, although the majority of study subjects were stable noncritically ill patients (elevated D-dimer). A hierarchical composite endpoint was composed of death, duration of hospitalization, and number of days with oxygen therapy at the end of 30 days. 615 patients were enrolled, randomized to therapeutic versus prophylactic anticoagulation in equal proportions. It was demonstrated that the therapeutic-dose anticoagulation did not improve prognosis and was related to an increased risk of major bleeding. Major bleeding was observed in 8% of patients receiving therapeutic-dose anticoagulation and in 2% of patients assigned to prophylactic-dose anticoagulation [45].

A retrospective observational study by Chow et al. enrolled 412 patients hospitalized for COVID-19, of whom 98 (23.7%) received additional acetylsalicylic acid (ASA) during the first 24 hours of hospitalization or within 7 days before admission. It was found that the use of ASA was associated with a lower frequency of ICU admission, mechanical ventilation, and in-hospital death [56]. There were no differences in terms of major bleeding or thrombosis between ASA users and non-users [56]. Another prospective randomized trial REMAP-CAP investigated standard therapy with or without 150 mg of ASA in hospitalized patients with COVID-19 [57]. The primary outcome was 28-day mortality. Almost all patients in the study group received thromboprophylaxis. 34% of patients were receiving thromboprophylaxis with extended-dose LMWH, 60% of patients were administered standard

dose LMWH, and 7% of patients were not receiving any thromboprophylaxis. A total of 7351 patients were randomly allocated to usual care plus ASA and 7541 were randomly allocated to usual care alone. The mortality rate was similar in both groups, 17% among patients in the ASA group vs. 17% of patients in the usual care group. No additional benefits, reduced mortality or lower risk of progressing to invasive mechanical ventilation were found in the group receiving usual care plus ASA. However, ASA was associated with a reduced duration of hospitalization of the patients who survived [57].

In patients with mild COVID-19 who do not require hospitalization, the general recommendations to reduce the risk of VTE should be kept in mind: drinking 1.5–2.0 l of water per day, and avoiding immobilization, tight clothing, and alcohol consumption. Routine thromboprophylaxis is not recommended in these patients [50, 58]. It can be considered individually in patients at high risk of VTE from other causes with a low risk of bleeding [50].

Selected patients with an increased risk of VTE hospitalized for COVID-19 may benefit from primary post-discharge thromboprophylaxis extended to 35 days after discharge. This approach is based on the results of the MICHELLE study [59]. The MICHELLE study enrolled patients hospitalized for COVID-19 with an increased risk of VTE, assessed using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) scale and D-dimer values [59]. These were patients at an increased risk of VTE (IMPROVE score of ≥4) or IMPROVE score of 2–3 and D-dimer >500 ng/mL at discharge [59]. The IMPROVE score predicts the risk of VTE within 3 months of follow-up, taking into account the following risk factors: age >60 years, history of VTE, known thrombophilia, lower limb paresis, immobilization >7 days before or during hospitalization, hospitalization at ICU, and active neoplastic disease [60, 61]. Patients were randomized to receive, at hospital discharge, 10 mg rivaroxaban or no anticoagulation for 35 days [59]. All patients received standard doses of thromboprophylaxis during hospitalization. The primary outcome, defined as a composite of symptomatic or fatal VTE, asymptomatic VTE (PE detected by CTPA or DVT detected by VUS), symptomatic ATE, and cardiovascular death at day 35 of observation occurred in 5 (5%) patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0.33, 95% CI 0.12–0.90; $p = 0.0293$). There were no major bleeding events in the thromboprophylaxis group [59].

Influence on Prognosis

Coexisting VTE and COVID-19 increase mortality in COVID-19 patients [2, 28, 41, 62].

Elevated D-dimer values were shown to be associated with an increased risk of death in COVID-19 patients, both with and without coexisting VTE [63]. Older age, high sequential organ failure assessment (SOFA) score, and D-dimer greater than 1000 μg/L early after admission are associated with a worse prognosis in COVID-19

patients, as reported already in the early days of the COVID-19 outbreak in Wuhan [38]. A follow-up study of 343 COVID-19 patients from Wuhan found that D-dimer ≥2000 μg/L predicted the risk of in-hospital death with a sensitivity of 92% and a specificity of 83% [39]. In another pooled analysis of 6 studies enrolling 1355 hospitalized COVID-19 patients, a D-dimer value of 3590 μg/L was argued to provide good discrimination of the risk of in-hospital death [64]. A large meta-analysis by Li et al. failed to identify a single optimal D-dimer cut-off point useful in estimating the prognosis of patients with COVID-19. Hoverer, it has been unequivocally demonstrated that D-dimer is a reliable prognostic biomarker in COVID-19, and that both 500 μg/L, 1000 μg/L, and 2000 μg/L cut-off points can be used in various populations to identify patients with an increased risk of in-hospital death [40].

Conclusions

Hospitalized COVID-19 patients are at an increased risk of thromboembolic complications. D-dimer elevation is often observed in patients with COVID-19 infection. D-dimer is considered a prognostic marker in these patients, but its specificity is lower when diagnosing venous thromboembolism. Thromboprophylaxis is recommended in all patients hospitalized for COVID-19, unless contraindications exist. Thromboembolic complications in hospitalized COVID-19 patients are associated with a poorer prognosis.

Acknowledgments The Pulmonary Hypertension Foundation supported editorial assistance of this chapter.

Conflict of Interest Authors have nothing to disclose.

References

1. Mondal S, Quintili AL, Karamchandani K, et al. Thromboembolic disease in COVID-19 patients: a brief narrative review. J Intensive Care. 2020;8:70. https://doi.org/10.1186/s40560-020-00483-y.
2. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7. https://doi.org/10.1016/j.thromres.2020.04.013.
3. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1995–2002. https://doi.org/10.1111/jth.14888.
4. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med. 2020;173:268–77. https://doi.org/10.7326/M20-2003.
5. Bosmuller H, Traxler S, Bitzer M, et al. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch. 2020;477:349–57. https://doi.org/10.1007/s00428-020-02881-x.

6. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9–14. https://doi.org/10.1016/j.thromres.2020.04.024.
7. Mackman N, Antoniak S, Wolberg AS, et al. Coagulation abnormalities and thrombosis in patients infected with SARS-CoV-2 and other pandemic viruses. Arterioscler Thromb Vasc Biol. 2020;40:2033–44. https://doi.org/10.1161/ATVBAHA.120.314514.
8. Porfidia A, Valeriani E, Pola R, et al. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. Thromb Res. 2020;196:67–74. https://doi.org/10.1016/j.thromres.2020.08.020.
9. Jimenez D, Garcia-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Chest. 2021;159:1182–96. https://doi.org/10.1016/j.chest.2020.11.005.
10. Yamashita Y, Maruyama Y, Satokawa H, et al. Incidence and clinical features of venous thromboembolism in hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan. Circ J. 2021;85:2208–14. https://doi.org/10.1253/circj.CJ-21-0169.
11. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax. 2021;76:412–20. https://doi.org/10.1136/thoraxjnl-2020-216243.
12. Obi AT, Tignanelli CJ, Jacobs BN, et al. Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients. J Vasc Surg Venous Lymphat Disord. 2019;7:317–24. https://doi.org/10.1016/j.jvsv.2018.08.010.
13. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362. https://doi.org/10.1016/j.jcv.2020.104362.
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;46:1089–98. https://doi.org/10.1007/s00134-020-06062-x.
15. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135–40. https://doi.org/10.1016/S1473-3099(20)30434-5.
16. Iba T, Levy JH, Warkentin TE, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17:1989–94. https://doi.org/10.1111/jth.14578.
17. Iba T, Levy JH, Connors JM, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24:360. https://doi.org/10.1186/s13054-020-03077-0.
18. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020;7:e575–82. https://doi.org/10.1016/S2352-3026(20)30216-7.
19. Canzano P, Brambilla M, Porro B, et al. Platelet and endothelial activation as potential mechanisms behind the thrombotic complications of COVID-19 patients. JACC Basic Transl Sci. 2021;6:202–18. https://doi.org/10.1016/j.jacbts.2020.12.009.
20. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364–74. https://doi.org/10.1007/s11427-020-1643-8.
21. McCracken IR, Saginc G, He L, et al. Lack of evidence of angiotensin-converting enzyme 2 expression and replicative infection by SARS-CoV-2 in human endothelial cells. Circulation. 2021;143:865–8. https://doi.org/10.1161/CIRCULATIONAHA.120.052824.
22. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. Blood. 2020;136:1317–29. https://doi.org/10.1182/blood.2020007214.
23. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res. 2019;181:77–83. https://doi.org/10.1016/j.thromres.2019.07.013.
24. Fara A, Mitrev Z, Rosalia RA, et al. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol. 2020;10:200160. https://doi.org/10.1098/rsob.200160.

25. Spyropoulos AC, Weitz JI. Hospitalized COVID-19 patients and venous thromboembolism: a perfect storm. Circulation. 2020;142:129–32. https://doi.org/10.1161/CIRCULATIONAHA.120.048020.
26. Wang J, Jiang M, Chen X, et al. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020;108:17–41. https://doi.org/10.1002/JLB.3COVR0520-272R.
27. Magro C, Mulvey JJ, Berlin D, et al. 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. https://doi.org/10.1016/j.trsl.2020.04.007.
28. Violi F, Pignatelli P, Cammisotto V, et al. COVID-19 and thrombosis: clinical features, mechanism of disease, and therapeutic implications. Kardiol Pol. 2021;79:1197–205. https://doi.org/10.33963/KP.a2021.0154.
29. Gill JC, Endres-Brooks J, Bauer PJ, et al. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood. 1987;69:1691–5.
30. Gerard C, Maggipinto G, Minon JM. COVID-19 and ABO blood group: another viewpoint. Br J Haematol. 2020;190:e93–4. https://doi.org/10.1111/bjh.16884.
31. 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;8:2450–7. https://doi.org/10.1111/j.1538-7836.2010.04044.x.
32. Cui LY, Cheng WW, Mou ZW, et al. Risk factors for pulmonary embolism in patients with COVID-19: a systemic review and meta-analysis. Int J Infect Dis. 2021;111:154–63. https://doi.org/10.1016/j.ijid.2021.08.017.
33. 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;18:1859–65. https://doi.org/10.1111/jth.14929.
34. Zochios V, Parhar K, Tunnicliffe W, et al. The right ventricle in ARDS. Chest. 2017;152:181–93. https://doi.org/10.1016/j.chest.2017.02.019.
35. Gorog DA, Storey RF, Gurbel PA, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol. 2022;19:475–95. https://doi.org/10.1038/s41569-021-00665-7.
36. Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19. Arterioscler Thromb Vasc Biol. 2020;40:2539–47. https://doi.org/10.1161/ATVBAHA.120.314872.
37. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.
38. 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;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
39. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18:1324–9. https://doi.org/10.1111/jth.14859.
40. Li Y, Deng Y, Ye L, et al. Clinical significance of plasma d-dimer in COVID-19 mortality. Front Med (Lausanne). 2021;8:638097. https://doi.org/10.3389/fmed.2021.638097.
41. Kollias A, Kyriakoulis KG, Lagou S, et al. Venous thromboembolism in COVID-19: a systematic review and meta-analysis. Vasc Med. 2021;26:415–25. https://doi.org/10.1177/1358863X21995566.
42. Mouhat B, Besutti M, Bouiller K, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. Eur Respir J. 2020;56:2001811. https://doi.org/10.1183/13993003.01811-2020.
43. Choi JJ, Wehmeyer GT, Li HA, et al. D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. Thromb Res. 2020;196:318–21. https://doi.org/10.1016/j.thromres.2020.09.022.

44. Kwee RM, Adams HJA, Kwee TC. Pulmonary embolism in patients with COVID-19 and value of D-dimer assessment: a meta-analysis. Eur Radiol. 2021;31:8168–86. https://doi.org/10.1007/s00330-021-08003-8.
45. Lopes RD, de Barros ESPGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet. 2021;397:2253–63. https://doi.org/10.1016/S0140-6736(21)01203-4.
46. Audo A, Bonato V, Cavozza C, et al. Acute pulmonary embolism in SARS-CoV-2 infection treated with surgical embolectomy. Ann Thorac Surg. 2020;110:e403–4. https://doi.org/10.1016/j.athoracsur.2020.04.013.
47. Nascimbene A, Basra SS, Dinh K, et al. Percutaneous thrombus removal in COVID-19-infected patient with pulmonary embolism. Methodist Debakey Cardiovasc J. 2021;17:e33–6. https://doi.org/10.14797/UUTH5836.
48. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation. 2020;142:184–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047430.
49. 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;158:1143–63. https://doi.org/10.1016/j.chest.2020.05.559.
50. Bikdeli B, Madhavan MV, Jimenez D, et al. 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;75:2950–73. https://doi.org/10.1016/j.jacc.2020.04.031.
51. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021;5:872–88. https://doi.org/10.1182/bloodadvances.2020003763.
52. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med. 2021;181:1612–20. https://doi.org/10.1001/jamainternmed.2021.6203.
53. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med. 2021;385:790–802. https://doi.org/10.1056/NEJMoa2105911.
54. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ. 2021;375:n2400. https://doi.org/10.1136/bmj.n2400.
55. The REMAP-CAP, ACTIV-4a, ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021;385:777–89. https://doi.org/10.1056/NEJMoa2103417.
56. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. Anesth Analg. 2021;132:930–41. https://doi.org/10.1213/ANE.0000000000005292.
57. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399:143–51. https://doi.org/10.1016/S0140-6736(21)01825-0.
58. Ozsu S, Gunay E, Konstantinides SV. A review of venous thromboembolism in COVID-19: a clinical perspective. Clin Respir J. 2021;15:506–12. https://doi.org/10.1111/crj.13330.
59. Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022;399:50–9. https://doi.org/10.1016/S0140-6736(21)02392-8.

60. Spyropoulos AC, Anderson FA Jr, FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest. 2011;140:706–14. https://doi.org/10.1378/chest.10-1944.
61. Rosenberg D, Eichorn A, Alarcon M, et al. External validation of the risk assessment model of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc. 2014;3:e001152. https://doi.org/10.1161/JAHA.114.001152.
62. Mansory EM, Srigunapalan S, Lazo-Langner A. Venous thromboembolism in hospitalized critical and noncritical COVID-19 patients: a systematic review and meta-analysis. TH Open. 2021;5:e286–94. https://doi.org/10.1055/s-0041-1730967.
63. Shah S, Shah K, Patel SB, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: a systematic review and meta-analysis. Cardiol Rev. 2020;28:295–302. https://doi.org/10.1097/CRD.0000000000000330.
64. Sakka M, Connors JM, Hekimian G, et al. Association between D-dimer levels and mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and pooled analysis. J Med Vasc. 2020;45:268–74. https://doi.org/10.1016/j.jdmv.2020.05.003.