Review

COVID-19 Associated Coagulopathy and Thrombotic Complications

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Abstract

The SARS-CoV-2 virus caused a global pandemic within weeks, causing hundreds of thousands of people infected. Many patients with severe COVID-19 present with coagulation abnormalities, including increased D-dimers and fibrinogen. This coagulopathy is associated with an increased risk of death. Furthermore, a substantial proportion of patients with severe COVID-19 develop sometimes unrecognized, venous, and arterial thromboembolic complications. A better understanding of COVID-19 pathophysiology, in particular hemostatic disorders, will help to choose appropriate treatment strategies. A rigorous thrombotic risk assessment and the implementation of a suitable anticoagulation strategy are required. We review here the characteristics of COVID-19 coagulation laboratory findings in affected patients, the incidence of thromboembolic events and their specificities, and potential therapeutic interventions.

Keywords

COVID-19, coagulopathy, D-Dimers, venous thrombosis, pulmonary embolism, thromboprophylaxis

From SARS-CoV-2 Infection to COVID-19 Disease

Since December 2019, cases of pneumonia linked to a new coronavirus have been reported in China.1 This coronavirus, named SARS-CoV-2, causes a disease called COVID-19 (COrona-VirusDisease of 2019). It is an emerging infectious disease of viral zoonosis type. In a context that has become epidemic within a few weeks, every health care professional has an essential role to play. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 pandemic.2

SARS-CoV-2 is characterized by its high contagiousness and its unusual potential lethality. Human-to-human transmission occurs via respiratory droplets, especially when people cough or sneeze, or via manual contact with a contaminated surface, as the virus can survive for several days on inert surfaces.3 The incubation period is between 2 and 14 days, with an average of 5 days. Asymptomatic patients are contaminating, and transmission of the virus is most important in the few days preceding symptoms and during the first days of illness.4,5 The diagnosis of COVID-19 disease is based on the performance of RT-PCR on a deep nasal swab. The negative predictive value depends on whether or not there are clinical signs and the penetration rate of the infection in the studied population.

When combined with a chest CT scan (without injection), the sensitivity increases to 97%. Radiological images or RT-PRC alone have a sensitivity of 88% and 59-85%, respectively.6

A significant proportion of infected people have no symptoms but can transmit the disease. The most frequent clinical signs of COVID-19 are those of acute pulmonary infection, ranging from paucisymptomatic forms or those suggestive of mild pneumonia to very severe forms with acute respiratory distress syndrome (ARDS), even multi-visceral failure and death. Forms with digestive symptoms (anorexia, nausea, diarrhea, abdominal pain) or initially non-febrile may be at the forefront. Other reported symptoms include headache, sore throat, and rhinorrhea. Sudden anosmia without nasal obstruction and dysgeusia are described from day 6-7, as well as frostbite or pseudo-frostbite. In the elderly, deceptive

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neurological forms are described (concentration disorders, confusion...).2.4.5.7.9

Overall, in the symptomatic forms, 80% of patients present mild to moderate signs, 15% will have a more severe form, and 5% will develop severe forms with ARDS and the need for mechanical ventilation. We can schematically identify 3 evolutionary phases: an initial phase (paucisymptomatic), an intermediate phase (pneumonia), and a final hyper-inflammatory phase (respiratory failure, vasoplegia, shock). If the initial phase is due to viral replication, progression to the following stages is associated with an uncontrolled immunological and inflammatory response (“cytokine storm”).10

The chronology of clinical worsening is not always stereotyped, with worsening of pneumonia, if occur, between day 7 and day 12 of progression but maybe earlier and extremely abrupt.7-11 Mortality in the intensive care unit is estimated at 30-60%.12

A report of 72.314 cases from the Chinese CDC revealed several risk factors associated with the worsening of the disease and mortality, including age over 70 years, cardiovascular disease, diabetes, hypertension, cancer, and chronic respiratory or renal failure.13 In Italy, among 355 deaths, the risk factors predictive of death included older age, a high SOFA score (Sequential Organ Failure Assessment), and the presence of comorbidities.14

On admission, many patients with pneumonia have polyneuropenia and deep lymphopenia, reported in 84% of cases. C reactive protein (CRP) levels increase in proportion to the severity of the disease.4.5 Some biological abnormalities are associated with a poorer prognosis, notably the depth of lymphopenia and a major increase in markers of inflammation (CRP, ferritin...). Other abnormalities are observed in severe forms such as increased transaminase, LDH, troponin, and acute renal failure. Several data show that coagulopathy is also central to the process of degradation of the clinical condition of patients.4.5.13.15

**Hemostasis Disorders During COVID-19**

During the Chinese epidemic, a “coagulopathy” was initially described in the first severe cases of SARS-CoV-2 infection, and this data has also been reported by European teams.5,13,15,20 The first described abnormalities are marked rise in D-Dimer (DD) and rather moderate thrombocytopenia, correlated with a higher risk of admission to intensive care and a higher death rate.5 Other hemostasis abnormalities are reported, less consistently or even contradictory, and their prognostic implications are more controversial, such as increased APTT and decreased PT/INR. Data published by Tang et al. from a cohort of 183 patients infected with SARS-CoV-2 and hospitalized revealed a mortality rate of 11.5%. The increase in DD was found in more than 71% of the patients who died from ARDS.17 Those patients showed evidence of overt disseminated intravascular coagulation (DIC) as defined by the validated International Society on Thrombosis and Haemostasis (ISTH) by the DIC score.21 However, the most common coagulopathy pattern observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and DD levels and should not be misinterpreted as DIC. Unlike the pattern seen in classic DIC from other sepsis or trauma, prolongation of the aPTT and/or PT is minimal, and thrombocytopenia is mild in COVID-19 patients.

The implication of this coagulopathy in the deterioration process of COVID-19 patients is confirmed by another Chinese study that analyzed clinical and biological data from a cohort of 201 patients with pneumonia. Patients who died (22%) from ARDS had a significant increase in DD compared to patients with ARDS who survived (890 vs. 5270 ng/mL; p = 0.001).18 The study by Zhou et al. compared 54 patients who died and 137 survivors; hospital mortality was associated in multivariate analysis with advanced age, SOFA score >5 and DD rate over 1000 ng/mL (p = 0.003). For a DD rate exceeding 1000 ng/mL the OR of death was 18.4 (p = 0.003).19 An analysis in Ireland noted a significant increase in DD in ICU patients (1003 vs. 804 ng/mL; p = 0.018). A recent pooled analysis, including 6 original studies among hospitalized patients with moderate to critical COVID-19 (n = 1355), indicates that DD levels are significantly associated with the risk of mortality in COVID-19 patients.22

Table 1 resumes data on the correlation between the rate of DD and the clinical evolution of hospitalized patients for COVID-19.

It is interesting to note that the importance of coagulopathy in the deterioration process of COVID-19 patients had already been documented in studies conducted on severe pulmonary forms with the 2 famous Coronaviruses previously described, the SARS-CoV (Severe Acute Respiratory Syndrome) in 2002-2003 in China and the MERS-CoV (Middle-East Respiratory Syndrome) in 2012-2013 in the Middle East.25 Among several biomarkers tested in these patients, coagulation abnormalities were not similar to those observed in SARS-CoV-2. Prolongation of APTT and significant thrombocytopenia were dominating the picture, and increased DD were reported but without being strongly correlated with poor prognosis.26

**Thrombotic Events and COVID-19**

Alterations in hemostasis and the resulting procoagulant nature during the COVID-19 are associated with a significant increase in thrombotic complications, which are currently better documented in the literature.

These thrombotic events have been little or no reported in the Chinese literature, possibly because of the importance of race and ethnicity. Indeed, epidemiological studies previously noted that the thromboembolic risk is 3 to 4 times lower in the Chinese population compared to the Caucasian population.27

The first descriptions report clinical findings in the field; with thrombotic complications becoming more frequent, the more severe the disease was. These descriptions varied from classic deep vein thrombosis (DVT) and pulmonary embolism (PE) to unusual thrombosis of central lines or arterial catheters, very early thromboses of extra-renal hemodialysis filters, and...
ECMO cannulas. Conversely, very few hemorrhagic complications have been reported.

Among the Chinese studies, the first reports a DVT rate of 25% of the 81 COVID-19 patients hospitalized in ICU. It should be noted that screening for DVT by ultrasound (US) of the lower limbs was carried out without, however, being systematic. These patients had a significantly higher rate of DD than patients without VTE (5200 ± 300 vs. 800 ± 1200 ng/mL, p < 0.001). A very recent publication reports a much higher figure in 2 other hospitals in Wuhan; 85.4% of the 48 patients hospitalized in the ICU, screened by venous lower legs US, had DVT.

The first European publications come from the Netherlands. Klok et al. reported a cumulative incidence of thrombotic complications of 31%, after a 7-day follow-up, in 184 patients with a severe form of COVID-19 in ICU. PE was the most common complication (n = 25, 81%). The presence of coagulopathy with PT prolongation >3 s and/or APTT >5 s was strongly associated with thrombotic events with an estimated HR of 4.1 (95% CI 1.9-9.1). Data from a second Dutch team included follow-up of 198 COVID-19 patients, 37% of whom were ICU patients. The overall incidence of VTE was 17%, of which 11% were symptomatic. Screening for DVT by US was performed in about 1/3 of the patients during their hospital stay. Pulmonary CT scan was performed only in patients with worsening hypoxia or markedly elevated DD. The cumulative VTE incidence at day 7 and day 14 was 15% and 34%. It was higher in ICU, reaching 48% of patients at day 14. In this study, after adjusting for age, sex, and ICU stays, VTE was associated with a 3-fold risk of death (HR: 2.9; 95% CI, 1.02-8.0). In France, Helms et al. reported on a prospective cohort of 150 COVID-19 patients admitted to the ICU for ARDS, an overall incidence of VTE disease of 18%, mostly PEs. Compared to a historical cohort of matched patients hospitalized for ARDS not related to COVID-19, the risk of PE was significantly higher in the COVID-19 cohort (OR: 6.2; 11.7 vs. 2.1%, p < 0.01). A second prospective study of 107 consecutive cases of ICU COVID-19 patients found a cumulative incidence of PE of 20.6%. The authors also noted 2 to 3 times more PE cases compared to a matched population, hospitalized in ICU in 2019 for severe non-COVID-19 pneumonia, or related to H1N1 infection.

From a radiological point of view, 3 studies analyzing pulmonary CT angiography performed in COVID-19 patients with respiratory difficulties noted an incidence of PE in 20%, 23%, and 30% of studied scans, respectively. Patients with PE were most often hospitalized in the ICU (74% of cases), on mechanical ventilation (65% of cases), and male (91% of cases). The authors, therefore, recommend changing practices at patient’s admission, favoring examination by pulmonary CT angiography, rather than chest CT, in cases of severe respiratory symptoms.

It is important to note that nearly 1/3 of patients were still hospitalized at the time of the publication of these studies, and it can be expected that the real incidence of VTE is underestimated. As an illustration, the updated study by Klok et al. notes a cumulative incidence of VTE with adjustment for deaths of 49%, including 65 cases of PE at 14-day follow-up, compared to 31% at 7-day follow-up. To summarize, given the heterogeneity of the studies and the variations of patient selection across studies and in addition to that a high risk for selection bias, it is difficult to determine a precise rate of VTE in COVID-19 patients. Overall, in observational reports, VTE is reported in 15 to 20% of patients and 30-35% in ICU. When using a systematic screen with leg ultrasound, the rate can be higher than 50% in ICU. Table 2 reported the main published data on VTE’s incidence during COVID-19, the detection methods, and the associated antithrombotic treatments.

Thus, the frequency of VTE in COVID-19 patients appears to be much higher than in other severe respiratory infections. In a meta-analysis of 7 studies, including 1.783 patients with ARDS from causes other than COVID-19, the incidence of VTE was 12.7%.

Also, several autopsy data highlighted the vascular dimension of the disease. The first studies found, in the

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**Table 1. Studies With the Correlation Between the Rate of DD and the Clinical Course of Patients Hospitalized for COVID-19.**

| Survivors/non-ICU | Deceased/ICU |
|-------------------|--------------|
| Huang C et al. | 500 (300-1300) | 2400 (600-14.400)* |
| Han H, et al. | 214 + 288 | 1960 + 3400 |
| Zhou F, et al. | 600 (300-1000) | 5200 (1500-21.000)** |
| Tang N, et al. | 610 (350-1290) | 2120 (770-5270)*** |
| Wu C, et al. | 1470 (500-944) | 4700 (1420-21.000)* |
| Wu Y, et al. | 520 (330-930) | 1160 (460-537)*** |
| Wu C, et al. | 510 (320-1080) | 1110 (510-4000)*** |
| Middendorp et al. | 600 (300-1300) | 4600 (1300-21.000)* |
| McDermott et al. | 1100 (700-1600) | 2000 (800-8100) |
| Fogarty et al | 804 (513-1290) | 1003 (536.5-1782)* |
| Wang | 1600 (1010-2850) | 4140 (1910-13.240)* |

*<0.001; **<0.0001; *** with or without ARDS; ICU: Intensive care unit.
advanced forms, pulmonary infarction and diffuse pulmonary, glomerular, and dermal micro thrombosis. A prospective study on 12 consecutive, complete autopsies of patients who died of SARS-CoV-2 infection noted 58% of VTE. Massive PE was the cause of death in 1/3 of the cases. Also, in all patients who developed DVT, both limbs were involved. A second study reported on an autopsy series of 21 COVID-19 patients, 4 cases of fatal PE, and generalized micro thrombosis in 3 other cases. Finally, a prospective series of 11 autopsies noted pulmonary artery thrombus in all patients, with segmental or sub-segmental involvement in 8 of them, despite thromboprophylaxis treatment in 10 of the 11 analyzed cases.

Issues with VTE Diagnosis in COVID-19 Patients
The conventional diagnostic approach with an assessment of the clinical probability of PE or VTE may not be efficient in this context. Consideration must be given to the occurrence of hypoxemia disproportionate to the pulmonary parenchymal involvement, unexplained acute right ventricular dysfunction,

| Table 2. Incidence of VTE and Characteristics of Studies in COVID-19 Patients. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | VTE             | Type of study and diagnostic method | Anticoagulant treatment |
| DVT (n) PE (n) DVT + PE (%)     | Type of study   | Prophylactic | Therapeutic |
| Critically ill (ICU)            |                |
| Cui et al. 28 n = 81            | 20 – 25%       | Retrospective US screening * | NA |
| Ren et al. 29 N = 48            | 5 proximal DVT – 85.4% | Retrospective US 100% | 99% – |
| Klock et al. 30,37 n = 184      | 1 DVT of legs 25 d7: 27% | Observational US 100% | 84% 9.2% |
| Helms et al. 32 n = 150         | 2 thrombosis of catheter 69 d14: 49% | Prospective US 100% | 70% 30% |
| Poissy et al. 33 n = 107        | – 22 20.6% | Observational US 100% | 99% 1% |
| Thomas et al. 38 n = 63         | 1 jugular thrombosis 10 27% | Observational US 100% | 100% – |
| Llitjios et al. 39 n = 26       | 18 DVT 6 69% | Retrospective US (J2 - J7): 100% | 31% 69% |
| Voicu et al. 40 n = 56          | 26 DVT 13 proximal / 13 distal 46% | Prospective US 100% D10 + D18 | 87% 13% |

Acutely ill (general inpatients ward)

|                                  | VTE             | Type of study and diagnostic method | Anticoagulant treatment |
|---------------------------------|-----------------|-----------------|-----------------|
| DVT (n) PE (n) DVT + PE (%)     | Type of study   | Prophylactic | Therapeutic |
| Mideltrp et al. 31 n = 198      | 13 proximal DVT 11 17% d7 / 34% d14 ICU: 39% d7/48% d14 | Observational ICU: 34% | 84% 9.4% |
| Lodigioni et al. 41 n = 388     | 1 upper limb thrombosis 5 DVT 10 21% | Retrospective ICU: 16% | 75% 23% |
| Demelo-Rodriguez et al. 42 n = 156 | 23 DVT / 1 proximal 7 bilateral thrombosis – 14.7% | Prospective / US DD ≥1000 ng/mL | 98% – |
| Zhang et al. 43 n = 159         | 66 DVT 23 proximal / 43 distal – 46.1% | Observational US for 143 patients | 37% – |

Pulmonary CT scan studies

|                                  | VTE             | Type of study and diagnostic method | Anticoagulant treatment |
|---------------------------------|-----------------|-----------------|-----------------|
| DVT (n) PE (n) DVT + PE (%)     | Type of study   | Prophylactic | Therapeutic |
| Leonard Lorat et al. 34 n = 106 | NA 32 30% ICU: 75% | Retrospective USI: 45% | 40% 6.5% |
| Grillet et al. 35 n = 100       | NA 23 23% ICU: 74% | Retrospective USI: 39% | NA |
| Poyiadi et al. 36 n = 328       | NA 72 22% | Retrospective US 100% | 23% – |

NA: not available; DVT: deep vein thrombosis; ICU: intensive care unit; d: days; US: ultrasounds of the legs.
Mechanisms of Coagulopathy: At the Crossroad of Inflammation and Coagulation

The mechanisms involved in the formation of thrombosis in COVID-19 are not yet completely elucidated. It is more of a coagulopathy than a true diffuse intravascular coagulation (DIC), as initially described. The coagulation abnormalities are different in patients with ARDS with COVID-19 vs. none COVID-19, with a higher DD rate, a higher fibrinogen level, and mild PT and APTT abnormalities. Changes in other parameters (platelet count, PT, APTT, fibrinogen, antithrombin, and protein C) were relatively modest. Ranucci et al. found the same specific procoagulant profile with a major increase in DD and fibrinogen correlated with an increase in IL-6.

Going back to the clinical and biological chronology of the disease course, the rapid worsening of respiratory symptoms is accompanied by an extremely marked increase in pro-inflammatory cytokines (IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α), commonly referred to as the “cytokine storm.” The explosive and uncontrolled release of these pro-inflammatory cytokines results in a significant increase in the biological parameters of inflammation (CRP, fibrinogen, ferritinemia, LDH). This acute inflammatory phenomenon can affect coagulation and fibrinolysis in several ways and amplify hypercoagulability. It has been demonstrated that excess IL-6 can induce tissue factor expression and thus initiate coagulation activation and thrombin generation.

Otherwise, infection with the SARS-CoV-2 directly or indirectly induces vascular endothelial dysfunction, thereby increasing the risk of thrombosis. The virus penetrates human target cells mainly by binding Angiotensin-Converting Enzyme-2, which is highly expressed in alveolar and cardiac cells, but also in the vascular endothelium. This is well demonstrated by the study by Varga et al., who found the presence of viral elements in the endothelial cell and an endothelial inflammation called “endothelitis.”

Theoretically, activation of these endothelial cells can have 2 main consequences. First, there is a well-coordinated innate immune response initially through recruitment and activation of immune cells, overexpression of chemotactic molecules (ICAM), adhesion molecules such as P-selectin, E-selectin, and activation of neutrophils, monocytes, and platelets. In parallel, when the endothelium is dysfunctional and inflammatory, it will express tissue factor, which is the key to the activation of the coagulation cascade. These 2 phenomena are intended to control infection and repair endothelial damage; they can become particularly deleterious if they are excessive and/or uncontrolled by the host. Failure to resolve the cytokine response (unclear mechanism) will cause the maintenance of endothelial activation and the coagulation cascade, thus lead to generalized endothelial dysfunction. The 2 phenomena of inflammation-hemostasis are, therefore, closely interconnected and mutually reinforced. It is thus a coagulopathy associated with severe forms of COVID-19 and significant inflammation, and authors propose the term “immunothrombosis” already introduced by Engelmann et al. in 2013.

It should be noted that a few cases of COVID-19 patients having developed antiphospholipid antibodies (aPL) presented with stroke and obstruction of several cerebral arteries, limb arteries. Other teams report high levels of aPL, found in up to 50% of cases, not correlated with thrombosis occurrence. These are anticardiolipin or anti-beta 2 glycoprotein 1 antibodies (Ab), of IgM, IgA and/or IgG isotype, with low or unreported titers. Lupus anticoagulant is also frequently found. These Ab may often appear in critical clinical states during various infections and could be considered as an epiphenomenon accompanying the endothelial activation and the immunoinflammatory storm. They appear to expose to thrombotic events rarely.

Antithrombotic Therapeutic Strategies

The Rationale for Antithrombotic Treatment

VTE has emerged as an essential consideration in the management of hospitalized patients with COVID-19, and
antithrombotic is surely a full-fledged treatment for COVID-19. The benefit of anticoagulant therapy has been reported by Tang et al. in 99 patients who received thromboprophylaxis with LMWH. Despite several significant limitations in this study, the authors concluded that the treatment with LMWH appeared to be associated with lower mortality in patients with a DD rate higher than 6 times the normal range or >3000 ng/mL (32.8% vs. 52.4%, p = 0.017).55 Anticoagulation benefits are also reported by another New York study involving nearly 3,000 severely hospitalized COVID-19 patients, 28% of whom were receiving thromboprophylaxis. Hospital mortality was significantly lower in patients under ventilation with anticoagulants vs. without anticoagulants (29.1% vs. 62.7%).66

Finally, in the updated follow-up of the Klok et al. cohort, prophylactic anticoagulation at admission was associated with fewer thrombosis at follow-up (HR 0.29, 95% CI 0.091-0.92).37

Of note, the proportion of critically ill COVID-19 patients on standard anticoagulant thromboprophylaxis dose that developed VTE ranged from 17 to 59% during hospital stay.28,43 None of the studies allows for comparison between different protocols or different regimens or different drugs. Because current evidence suggests failure of thromboprophylaxis in critically ill COVID-19 patients and in randomized controlled trials the incidence of VTE seems higher than in critically ill non COVID-19 patients,44,67 many institutions have adopted prophylaxis protocols with so-called “reinforced doses.”

The “standard” preventive anticoagulation doses may be insufficient, particularly in patients with high DD levels, high BMI, or intensive care hospitalization. The presence of a significant inflammatory state and hypercoagulability leads to non-specific binding of heparin chains to inflammatory proteins and an acquired antithrombin deficiency, thus reducing its bioavailability. These phenomena could compromise antithrombotic efficacy and make the anticoagulant activity less predictable.68 It is interesting to note in the study by Ranucci et al. that an increase in the doses of heparin in patients with a procoagulant profile was accompanied by a significant decrease in DD and fibrinogen.54

Some have advocated using empiric full dose therapeutic-dose anticoagulation for the critically ill hospitalized COVID-19 patients with coagulopathy; however, the scientific evidence in favor of this therapeutic approach is currently limited, based on subgroup analyses of retrospective series and/or monocentric cohorts and is therefore not consensual. This hypothesis is currently being tested in several ongoing studies (NCT04372589, NCT04367831, NCT04345848, NCT04366960).

DOACs have demonstrated mixed results with regard to inpatient and postdischarge prophylaxis for VTE.69,70 They should be considered with caution in COVID-19 patients. Many of these patients will likely be receiving concomitant therapy (antiviral agents or other investigational treatments) that can significantly interfere with DOAC therapy.71

### Regimen and Duration for Anticoagulant Thromboprophylaxis

Based on the data reported in the previous paragraphs, it is essential to consider COVID-19 patients as high-risk or even very high-risk thrombotic patients at the time of hospitalization.72 The assessment of this risk should be dynamic, and it is recommended to repeat it whenever the patient’s clinical status changes. This thrombotic risk assessment should also include biological markers such as DD and fibrinogen levels, the sudden increase of which is an indicator of the imminent worsening of the disease.72-76 Then there was an urgent need for practical guidance regarding the prevention of VTE in hospitalized COVID-19 patients.4-70

In COVID-19 patients without significant comorbidities treated as outpatients, routine preventive anticoagulation is not recommended. The same is true for quarantined individuals in general, in the absence of a significant risk factor for VTE. Patients should avoid sedentary lifestyles, dehydration, and be encouraged to remain active with regular mobilization during isolation. It is always recommended to identify possible candidates for outpatient thromboprophylaxis based on their clinical profile and medical history (overweight, comorbidities, cardiovascular risk factors, immobilization, previous DVT, hormone therapy, familial thrombophilia, active cancer, etc.).

All hospitalized patients with confirmed SARS-CoV-2 infection should receive pharmacologic thromboprophylaxis with LMWH or UFH on admission for severe renal failure, regardless of the reason for hospitalization.77,78

For patients with moderate COVID-19, it should be kept in mind that because of the presence of a significant inflammation (which is not included in the various thrombotic risk prediction scores such as the PADOU79 or IMPROVE80 scores), the risk of VTE is even higher. In this assessment of risk level, it should also be noted that obesity is a major risk factor in these patients. Indeed, various data support a negative impact of obesity on the prognosis of severe forms of COVID-19. In a retrospective study from France, after multivariate analysis, the OR of ICU admission in the most obese patients was estimated at 7 (BMI >35 kg/m² vs. ≤25 kg/m²; 95% CI, p = 0.02).81 Patients with a BMI greater than 30 kg/m² have a higher risk of PE of 2.7 (95% CI 1.3-5.5; p < 0.006).36 The standard dose of thromboprophylaxis should be adjusted if the patient is overweight/obese.82,83

In severe COVID-19 patients admitted to the ICU or under ventilation, the thrombotic risk is very high, and pharmacological prevention is mandatory. There is currently no consensus on the optimal anticoagulation dosage for these patients. It is clear that in the context of the hypercoagulability observed during severe COVID-19, a standard dose thromboprophylaxis may be considered insufficient given the significant thrombotic over-risk observed. Therefore, most expert groups propose at least thromboprophylaxis at “increased doses” adjusted “for the BMI.” Early diagnosis of coagulopathy identified by a significant and abrupt rise in the rate of DD (and fibrinogen), would also help adapt the management of these patients. Those different thromboprophylaxis protocols are detailed in Table 3.
When UFH is used, monitoring is essential, as it has an unpredictable dose-response and a narrow therapeutic window. Anti-Xa levels best manage it, aPTT should be avoided in this context because it does not reflect the anti-Xa effect. Most VTE events occur in the post-hospital discharge period, with the first 3 weeks being associated with a greater than 5-fold increased risk in fatal PE. Recent data also supports that a modified IMPROVE VTE score using established DD cut-off (>2 times ULN) identifies patients at an almost 3-fold higher risk for VTE in whom there is a significant benefit for extended-duration thromboprophylaxis. In the absence of COVID-19-specific data, it is reasonable to consider extended-duration thromboprophylaxis for at least 2 weeks after hospital discharge or after normalizing biological abnormalities in patients at low risk of bleeding.

Finally, in patients at high bleeding risk or with active bleeding, contraindicating temporarily pharmacologic thromboprophylaxis, intermittent pneumatic compression is recommended in patients in ICU.

**Take-Home Messages**

- SARS-Cov-2 infection is likely to predispose to the development of VTE, especially in severe disease. There is a high incidence of thrombotic events in hospitalized patients, which can be estimated at 15-30%, which is even higher when patients are in ICU.
- There is a clear hypercoagulability in severe forms of COVID-19, and a high level of DD (>1000 ng/mL) is associated with aggravation of pneumonia, progression to ARDS, and is a predictor of thrombotic complications and death. This coagulopathy accompanies and complicates a major inflammatory condition.
- Careful and dynamic thrombotic risk assessment should be performed in all COVID-19 patients, whether hospitalized or not. This assessment includes classic thrombotic risk factors, but also biological parameters such as DD and CRP.
- Preventive anticoagulation is always indicated in hospitalized patients. Its intensity depends on the level of risk assessed. The optimal anticoagulation strategies, including adapted prophylaxis, are still on debate. Therapeutic antithrombotic treatment could be considered in the event of admission to the ICU or significant hypercoagulability.

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