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COVID-19 INFECTION AND THROMBOTIC RISK

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Abstract

COVID-19 infection (SARS-CoV-2) is accompanied by a risk of venous and arterial thrombosis. The marked inflammation in severe forms is accompanied by an increase in D-dimers. The mechanism of hypercoagulability is not precisely known. Coagulation abnormalities would be comparable to those of disseminated intravascular coagulation (DIC) with thrombocytopenia, consumption of coagulation proteins. COVID infection is an inflammatory and infectious condition that promotes venous thromboembolic disease. All learned societies recommend anticoagulation based on assessing the risk of thrombosis, testing for the existence of risk factors and the severity of COVID-19.

KEYWORDS: Covid 19- thrombosis - thrombotic risk - anticoagulation

Introduction:

The manifestations reported during COVID-19 infection are very varied, including an inflammatory state, which can be very important and lead to a "cytokineic storm" and a prothrombotic state, causing thrombosis, essentially venous. This inflammation causes a lesion and activation of the microvascular endothelium, probably at the origin of the pulmonary or renal manifestations of the pathology. COVID-19 mortality has been attributed to secondary hypoxemia of acute respiratory distress syndrome (ARDS), and thromboembolic events may also contribute.

Changes in coagulation during COVID-19 suggest the presence of a hypercoagulability state with essentially an increase in D-concentration dimers, a relatively modest decrease in platelets and an extension of prothrombin time, which could increase the risk of thromboembolic complications. Monitoring the parameters of hemostasis is essential for the treatment of patients, since some abnormalities are associated with the most severe clinical forms and with an increased thrombotic risk. GIHP (interest group in perioperative hemostasis) and GFHT (French group of studies on hemostasis and thrombosis), made proposals on the prevention of thromboembolic disease and the modalities of treatment and biological monitoring of hemostasis in patients with COVID-19. [1]

Mechanisms of coagulopathy

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by coronavirus 2 severe acute respiratory syndrome (SARS-CoV-2). The impact of COVID-19 on many organic systems, including the respiratory tract, has led to increasing morbidity and mortality worldwide. Mortality due to COVID-19 can be largely attributed to secondary hypoxemia of acute respiratory distress syndrome (ARDS), there is a growing suspicion that thromboembolic events may also contribute to the overall picture. as described in the article published by Cui S et al [31].

SARS-CoV-2 invades host cells by binding its surface-peak protein to the cell receptor of the angiotensin 2 conversion enzyme (ACE2), which is widely expressed in arterial and venous endothelial cells, pulmonary type II alveolar cells, arterial smooth muscle cells in most organs, small intestine enterocytes, neural cortex and brainstem. [2][3]

The multiple localization of the ACE2 receptors explains the involvement of different organs in particular arterial and venous endothelial cells and coagulation are not spared. [4]

Inflammation-induced thrombosis is a well-known entity and is an essential component of the immune system's response to injury and infection. Systemic inflammation is a powerful prothrombotic stimulus, which can increase platelet activity and procoagulant factors, lower natural anticoagulants and inhibit fibrinolytic activity, resulting in coagulation activation and hypercoagulability. The complex interactions between inflammation and hemostasis involve innate immunity, pro-inflammatory cytokines, chemokines, adhesion molecules, expression of tissue factor, platelet and endothelial activation, and microparticles. In turn, coagulation also increases inflammation. Activated coagulation products, including thrombin, FXa, fibrin and TF-FVIIa complex by activation of protease-activated receptors. [5]

Mild Covid-19 can quickly progress to acute lung injury, ARDS, sepsis and multiple organ failure. A potential etiology of the sudden worsening of the disease is cytokine release syndrome (SRC) [6]. Numerous studies have shown that there is excessive production of inflammatory cytokines including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, IFN-γ, IFN-γ –Inducible 10 protein, monocyte 1 chemoattractive protein, granulocyte colony stimulation factor, 1a and TNF-a macrophage inflammatory protein in COVID-19 patients under critical conditions. [7] [8][9] [10]

Endothelial cells play a crucial role in normal hemostasis by maintaining vascular wall integrity and expressing platelet inhibitors (i.e., nitric oxide and prostaglandin I2) and various anticoagulants such as tissue factor pathway inhibitor, thrombomodulin, endothelial C-protein receptor and heparin- such as proteoglycans [11].

In endothelial cells, the Weibel-Palade bodies store VWF, P-selectin, angiopoietin-2, plasminogen tissue activator (tPA) and endothelin-1, which are active participants in

platelet adhesion, leukocyte recruitment, modulation of inflammation, fibrinolysis and vasoconstriction [12]. The disruption and dysfunction of endothelial cells leads to an increase in vascular wall permeability in pulmonary microvascularization, an essential step in thrombo-inflammatory that results in ventilation and infusion mismatch, and a clinical phenotype of refractory ARDS, and eventually systemic vasculopathy in COVID-19. A direct viral infection of endothelial cells, diffuse endothelial inflammation of various organs have been demonstrated in a series of patients with COVID-19[13].

The mechanism by which SARS-CoV-2 infection induces hypercoagulability is not precisely known. Inflammation is very marked in COVID infection, especially in severe forms, leading to D-dimer elevations. Recent articles have described hypercoagulability in patients with COVID-19 [14] [15].

Venous thromboembolic disease

The presence of microthrombotic disease in the pulmonary arteries [16] and the signs of coagulopathy associated with COVID-19 led doctors to consider pulmonary embolism (PE) as the etiology of patients with acute respiratory impairment. In COVID-19 patient case reports, pulmonary embolism (PE) has been identified in patients without risk factors for venous thromboembolism (VTE) [17]. A series of post-mortem autopsies revealed that venous thromboembolism was present in 7 of the 12 (58%) COVID-19 patients, with PE being the direct cause of death in 4 (33%) [18]. Similarly, alveolar autopsy damage was reported in 2 other studies [19]. Zhang et al. reported pulmonary microvascular thrombosis and necrosis in the mediastinal lymph nodes and spleen, and thrombosis of small vessels in multiple organs in 4 COVID-19 patients. Microvascular thrombus was characteristic of COVID-19 versus SARS1 [20].

A series of cases in France analyzed the first 107 COVID-19 patients admitted to the ICU from a single centre and compared PE rates to those of patients admitted to the same ICU a year earlier and those of patients admitted for influenza. At the time of analysis, 22 (20.6%) of COVID-19 patients had a PE, with a median diagnosis time of 6 days. In comparison, the general intensive care population a year earlier and the influenza population had CE rates of 6.1% and 7.5%, respectively. The cumulative impact of 15-day PE in the COVID-19 population was 20.4%. Of the 22 patients diagnosed with PE, 20 received prophylactic doses of HBPM or HNF, while one patient was on fluindione with therapeutic INR and another was on therapeutic HNF for atrial fibrillation [21].

Arterial thrombosis

With respect to cerebrovascular disease, a series of New York cases described 5 patients with SARS-CoV-2, all under the age of 50, who had acute ischemic stroke. Only one had a history of stroke[22]. A retrospective study of 214 COVID-19 patients admitted to hospital was conducted in Wuhan. Six (2.8%) patients had an acute stroke, 5 of whom had "severe" illness. Although no definition was provided, patients with "severe" disease had a higher frequency of comorbidities, including hypertension, and were on average older [23]. Reports from other groups are very similar with a reported stroke between 2.7% and 3.8% of patients [24] [25] [26] [28] [29]. Overall, all studies included 973 patients with a pooled proportion (random effect model) of 3.5% (95% CI 2.4-4.8) with no statistical heterogeneity.

Clotting markers

Many patients with severe COVID-19 have coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. but COVID-19 has distinct characteristics [30].

Coagulopathy in patients with COVID-19 is associated with an increased risk of death. [31] In addition, the relevance of COVID-19 coagulation abnormalities is becoming clearer as a substantial proportion of patients with severe COVID-19 develop venous and arterial thromboembolic complications, sometimes unrecognized [32] [33] [34].

D-dimers were identified early on as predictors of mortality [35]. The very high increase in Ddimers during COVID-19 can be explained by various mechanisms: advanced age, major inflammation, acute pulmonary aggression with intra-alveolar deposits of fibrin probably at the origin of D-dimers production in situ [36]. This increase is not specific to COVID-19 as elevated D-dimer levels are similar during complicated sepsis pneumonia and induced by other pathogens. Although it is recognized that D-dimers are useful in identifying patients at risk of severe COVID-19 or even mortality [35], they cannot be used for diagnostic exclusion from PE because their values are highly variable according to the methods used and their negative predictive value at the usual thresholds (500 threshold, age-adjusted threshold or clinical probability as in YEARS or PEG-eD algorithms) is very poor. Studies are underway to build a decision algorithm using D-dimers specifically for COVID-19 patients. Furthermore, it is not recommended to use D-dimers in common practice to "follow" a possible state of hypercoagulability or decide on a treatment [40]. In parallel with D-dimers, an increased proportion of antiphospholipid antibodies [37] have been identified as increasing the risk of thrombosis. However, it is well known that the positivity of these antibodies is common during certain viral infections which, by activating the immune system, can cause transient and non-pathogenic antibodies to emerge [38]. A recent study appears to confirm this theory with respect to antiphospholipid antibodies during COVID-19 [39].

Patients admitted to intensive care units (ICUs) were found to have significantly higher median D-dimer concentrations (2 4 mg / L, IQR 0 6–14 4) than patients who received no ICU care (0 5 mg / L, 0 3–0 8) [41] [42]. In consecutive COVID-19 patients, only about 5% of patients had platelet counts below 100 10 9 cells per L. However, mild thrombocytopenia (platelet counts <150 10 9 cells per L) can be found in 70-95% of patients with severe COVID-19. COVID-19-associated thrombocytopenia has not been shown to be an important predictor of disease progression or adverse outcome [33].

Mean fibrinogen concentrations in patients with COVID-19 are at the upper limits of normal, likely as an acute phase response. However, a sudden decrease in plasma

fibrinogen at concentrations below 0 g/L was observed shortly before death in a number of COVID-19 patients in China [31].

Inflammatory syndrome contributes to the elevation of fibrinogen. Its correlation with the risk of thrombosis would be possible. Thus, the perioperative hemostasis (HPGI) interest group considers that a threshold of 8 g/L would be associated with a very high risk of ED accidents in COVID-19. Clinical findings report much higher rates in this infection. [43]

Coagulation changes associated with COVID-19 suggest the presence of a hypercoagulable condition that could increase the risk of thromboembolic complications. Immobilization and vascular damage are other factors that can increase the risk of thrombosis. In severely ill patients, the incidence of thromboembolic complications ranges from 5% to 15%. Initial cohort studies show that the incidence of thromboembolic complications in COVID-19 patients is 35-45%. Some people have also suggested that pulmonary embolism may be involved in the rapid respiratory deterioration seen in some patients, but for practical reasons, it is not always possible to perform adequate objective diagnostic tests (e.g. CT angiography) [44].

Arterial thrombosis was also reported. Of 241 patients, 5.7% had acute cerebrovascular disease [45]. In these patients, an unusual association of antiphospholipid antibodies with the presence of anti-cardiolipid IgA and anti-β2 glycoprotein I IgA and IgG antibodies was detected, raising the question of the role of antiphospholipid antibodies. However, these were antibodies detected on one occasion and no titre was given, so by definition they did not meet the criteria for antiphospholipid syndrome.

Thrombotic and anticoagulation risk assessment

Hypercoagulability is an important feature of inflammation. Pro-inflammatory cytokines are critically involved in abnormal clot formation and platelet hyperactivation and also play an important role in the downward regulation of important physiological anticoagulant pathways [46] [47].

Older patients and those with comorbidities are more likely to develop serious complications from COVID-19 infection and are at higher risk for thrombosis [48].

Several studies have found a decrease in mortality among COVID-19 patients who received anticoagulation during hospitalization compared to those who did not [49] [50]. Most of the main societal guidelines and recommendations (ISTH-IG (International Society on Thrombosis and Haemostasis interim guidance, ACF (Anticoagulation Forum), CDC (Centers for Disease Control and Prevention) and ASH (American Society of Hematology)) advise to hold anticoagulation in patients who are actively bleeding or who are severely thrombocytopenic. ISTH-IG recommends maintaining prophylactic HBPM anticoagulation for patients with platelet counts below 25 10 9 / L. ASH states that therapeutic anticoagulation should be maintained if platelet counts <30–50 10 9 / L or fibrinogen <1,0 g / L, and prophylactic anticoagulation should only occur if platelet count <25 10 9 / L or fibrinogen <0.5 g / L. SCC-ISTH does not recommend a specific platelet level to maintain anticoagulation, but reports that 50% of their respondents report holding for a platelet count <25 10 9/ L. Although the CDC

and ACF (Anticoagulation Forum) recommend maintaining prophylactic anticoagulation in severely thrombocytopenic patients, Nor do they recommend a particular platelet count threshold.

The CACP (American College of Chest Physicians) does not make any specific recommendations regarding anticoagulation performance. ACC (American College of Cardiology) reports that in patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation who develop a suspected or confirmed DIC with manifest bleeding, it is reasonable to consider the indication of anticoagulation and the risk of bleeding to adjust the dose or stop anticoagulation. The majority of their authors recommend reducing the intensity of anticoagulation unless there is an excessively high risk of thrombosis [51].

The International Society of Thrombosis and Hemostasis (ISTH) recently published on the detection and treatment of coagulopathy in COVID-19. He suggests that patients with a high d-dimer (that is, arbitrarily defined as an increase of 3 to 4 times) should be hospitalized. Low molecular weight heparin should be considered in all patients requiring hospitalization for COVID-19 infection unless contraindicated. [33].

In patients hospitalized with COVID-19, the prevention of thromboembolic disease with PMHB is the preferred option, but it is likely that medically validated dosages are frequently inadequate, especially in severe forms and in cases of obesity. Surveillance of hemostasis, is essential in the conduct of treatment, because its abnormalities (increase in the concentration of D-dimers) are associated with the most severe forms of the disease and a high thrombotic risk.

Early detection of these potentially predictive abnormalities can therefore contribute to an optimized prescription of anticoagulant treatment. In this context, and despite the absence of published evidence, the GIHP (Perioperative Hemostasis Interest Group) and the GFHT (French Study Group on Hemostasis and Thrombosis), have drafted proposals on the prevention of thromboembolic disease and modalities of biological monitoring of hemostasis in hospitalized COVID-19 patients to provide early decision support. GIHP (Perioperative Hemostasis Interest Group) and GFHT (French Study Group on Hemostasis and Thrombosis) [52].

These proposals are regularly reviewed based on our evolving knowledge of COVID-19 and include:

A. Define the level of risk of thrombosis in patients with covid-19

1. Research all COVID-19 patients for overabunded major thromboembolic risk factors (RDFs), including: active cancer (treatment within the last 6 months), recent personal history (< 2 years) of thromboembolic event.

Other risk factors can be considered (age >70, prolonged bed rest, postpartum, combined oral contraception, etc.).

2. Identify and characterize thrombotic risk factors that appear to be determinants of COVID-19

- Severity of COVID-19 reflected by treatment intensity: no oxygen therapy

(O2), oxygen therapy, high-throughput nasal oxygen therapy (ONHD) or artificial ventilation.

- Body Mass Index (BMI)

3. Deduce 4 levels of thromboembolic risk (table):

a. Low risk: non-hospitalized patient with BMI < 30 kg/m2 without over-added FDR.

b. Intermediate risk: BMI < 30 kg/m2 with or without over-added FDR, without the need for OHND or artificial ventilation.

c. High Risk:

- BMI < 30 kg/m2 with or without overadded FDR, under ONHD or artificial ventilation

- BMI > 30 kg/m2 without overadded FDR

- BMI > 30 kg/m2 with overadded FDR, without the need for OHND or artificial ventilation

d. Very high risk:

- BMI > 30 kg/m2 with overadded FDR, under ONHD or artificial ventilation

- ECMO (venous or venous arterial)

- Iterative or unusual catheter thromboses

- Extra-renal purification filter thromboses

- Marked inflammatory syndrome and/or hypercoagulability (e.g. fibrinogen > 8 g/L or D-Dimers > 3 µg/ml or 3000 ng/ml).

B. Prescribing anticoagulant therapy in patients with covid-19

1. In all hospitalized patients, it is proposed that oral anticoagulant, AVK or AOD (risk of instability and drug interactions) treatments be relayed through curative heparin therapy.

2. For intermediate thrombotic risk, it is proposed to prescribe prophylaxis with low molecular weight heparin (LMWH): for example, enoxaparin 4000 IU/24h SC or tinzaparin 3500 IU/24h SC. Fondaparinux 2.5 mg/24h SC is an alternative if the creatinine clearance (Clcr) is greater than 50 ml/min. In the presence of severe renal failure, an alternative to calciparin may be proposed: enoxaparine 2000UI/24h SC for Clcr between 15 and 30 ml/min or tinzaparine 3500 UI/24h SC for Clearence between 20 and 30 ml/min.

3. In patients treated with standard prophylactic LMWH, it is recommended that anti-Xa activity is NOT monitored.

4. In cases of high thrombotic risk, it is proposed to prescribe HBPM-enhanced prophylaxis at enoxaparin 4000 IU/12h SC or 6000 IU/12h SC if weight > 120 kg. In cases of renal failure (Clcr < 30ml/min), it is proposed to prescribe undivided heparin (UFH) at 200 IU/kg/24 h.

5. In patients treated with a dose of LMWH greater than the standard prophylactic dose, it is proposed to monitor anti-Xa activity 4 hours after the 3rd injection and then regularly in renal failure for overdose (variable threshold value according to the HBPM) exposing to a higher risk of bleeding.

6. For very high thrombotic risk, it is proposed to prescribe curative heparin therapy with PMHB, for example enoxaparin at 100 IU/kg/12h SC, or HNF at 500 IU/kg/24h for severe renal impairment.

7. In all obese patients (BMI > 30 kg/m2), the thrombotic risk being high or very high, the proposed heparin dosages are:

a. Enoxaparine 4000 IU/12h or 6000 IU/12h if weight > 120 kg.

b. with over-added FDR and ONHD or artificial ventilation: enoxaparine 100 UI/kg (Actual Weight) /12h SC not exceeding 10,000 IU/12h or HNF 500 IU/kg/24h.

8. In all HNF patients, control anti-Xa activity at least every 48 hours and after each dose change, which should be maintained if the risk of bleeding is controlled between 0.3 and 0.5 IU/ml during reinforced prophylactic treatment (starting dose 200 IU/kg/24h), and between 0.5 and 0.7 IU/ml during curative treatment (starting dose 500 IU/kg/24h).

9. The introduction of ECMO (venous or venous arterial) immediately exposes to a very high thrombotic risk. It is therefore proposed to prescribe curative anticoagulation by HNF upon initiation of ECMO (regardless of ECMO flow rate), for an anti-Xa objective between 0.5 and 0.7 IU/mL.

10. If marked inflammatory or hypercoagulability syndrome (for example: fibrinogen > 8 g/L or D-dimer > 3 µg/ml or 3000 ng/ml) or rapid increase in D-concentrationDimers, a curative heparinotherapy is proposed even in the absence of clinical thrombosis taking into account the risk of bleeding.

11. On HNF, it is recommended to monitor platelet counts at least every 48 hours. A decrease of more than 40% between the 4th and 14th day of treatment requires a DIC assessment and the search for heparin-induced thrombocytopenia.

12. In the event of multivisceral failure, or consumption coagulopathy with sudden decrease in fibrinogen concentration, platelet count and V-factor, it is proposed to reassess the dosage of heparin therapy, these events are associated with increased risk of bleeding.

13. The duration and intensity of thromboprophylaxis will be re-evaluated based on the severity of the infection and risk factors.

Echodoppler's Place in Covid 19:

Doppler ultrasound (ED) of the veins of the lower limbs is an examination that explores not only femoral and popliteal veins but also sural veins, iliac veins bilaterally and the inferior vena cava [53]. The length of the examination naturally exposes the examiner to infectious risk. An alternative considered for the detection of DVT of the

lower limbs in COVID-19 patients, especially in resuscitation is the ED called 4 compression points (femoral veins common to the groin and popliteal vein in the right and left popliteal hollow). However, this technique used in emergency services is not fully validated [54]. The priority for the examiner therefore remains to minimize the duration of the examination and therefore the exposure to the infectious risk.

According to the GIHP (Perioperative Hemostasis Interest Group) and the GFHT (French Group of Studies on Hemostasis and Thrombosis), A venous echo-doppler of the lower limbs is to be considered during any unexplained clinical aggravation, or in case of sudden rise of D-Dimers.

Conclusion

Infection with the SARS-CoV-2 virus appears to induce an unusual prothrombotic condition of multifactorial origin, the paroxysm of which is observed in the most seriously affected patients, SI. A very careful thromboprophylaxis and a low detection threshold of symptoms and signs of MTEV are necessary.

Despite the incredible momentum in research, many issues remain unresolved, such as the diagnostic algorithm for VTE during COVID-19 or the best anticoagulation strategy in hospitalized patients. With respect to the management of patients who have experienced thrombosis during COVID-19, it will be important for them to be able to benefit from specific follow-up to determine the modalities of antithrombotic treatment.

Declaration of interest links: The authors declare that they have no interest links.

References:

[1]. Fatimah Al-Ani, a,1 Samer Chehade, a,1 and Alejandro Lazo-Langnera,b, Thrombosis risk associated with COVID-19 infection. A scoping review Thromb Res. 2020 Aug; 192: 152–160.thromres.2020.05.039

[2]. Hamming JE, Timens W, Bulthuis ML, Lely À, Navis G, van Goor H. Distribution tissulaire de la protéine ACE2, le récepteur fonctionnel du coronavirus du SRAS : une première étape dans la compréhension de la pathogenèse du SRAS. J Pathol. 2004 ; 203 (2): 631- 637.

[3]. Ferrari MF, Raizada MK, Fior-Chadi DR. La nicotine module le système rénine-angiotensine des neurones en culture et des cellules gliales des zones cérébrales cardiovasculaires de Wistar Kyoto et des rats spontanément hypertendus. J Mol Neurosci. 2007 ; 33 (3): 284- 293.

[4]. Giannis RÉ, Ziogas IA, Gianni P. Troubles de la coagulation chez les patients infectés par un coronavirus : COVID-19, SRAS-CoV-1, MERS-CoV et leçons du passé. J Clin Virol. 2020 ; 127 : 104362.et le système immunitaire 4. YQ, Wang B, Mao J. La pathogenèse et le traitement de la 'Cytokine Storm' dans COVID-19. J Infect. 2020 ; 80 (6): 607- 613.

[5]. Li Z, Yin M, Zhang H, et coll. Le BMX réprime la perméabilité endothéliale médiée par la thrombine-PAR1 et les fuites vasculaires pendant la septicémie précoce. Circ Res. 2020 ; 126 (4): 471- 485.

[6]. Mehta P, McAuley DF, marron M, et coll. COVID-19 : considérez les syndromes de tempête de cytokines et l'immunosuppression. Lancette. 2020 ; 395 (10229): 1033-1034.

[7]. Huang C, Wang Oui, Li X, et coll. Caractéristiques cliniques des patients infectés par le nouveau coronavirus 2019 à Wuhan, Chine. Lancette. 2020 ; 395 (10223): 497-506.

[8]. Qin C, Zhou L, Hu Z, et coll. Dysrégulation de la réponse immunitaire chez les patients atteints de COVID-19 à Wuhan, Chine [Publié en ligne avant impression Mars 12, 2020].

[9]. Mehta P, McAuley DF, marron M, et coll. COVID-19 : considérez les syndromes de tempête de cytokines et l'immunosuppression. Lancette. 2020 ; 395 (10229) : 1033-1034.

[10]. Zhang W, Zhao Oui, Zhang F, et coll. L'utilisation d'anti-inflammatoires dans le traitement des personnes atteintes de maladie grave à coronavirus 2019 (COVID-19) : les points de vue des immunologistes cliniques de Chine. Clin Immunol. 2020 ; 214 : 108393.

[11]. Esmon CT, Esmon NL. Le lien entre les caractéristiques vasculaires et la thrombose. Annu Rev Physiol. 2011 ; 73 : 503- 514.

[12]. Yau JW, Teoh H, Verma S. Contrôle des cellules endothéliales de la thrombose. Troubles cardiovasculaires BMC. 2015 ; 15 : 130.

[13] Varga Z, Flammer UN J, Steiger P, et coll. Infection des cellules endothéliales et endothéliite dans COVID-19. Lancette. 2020 ; 395 (10234) : 1417- 1418.

[14]. Tang N, Li D, Wang X, Sun Z. Des paramètres de coagulation anormaux sont associés à un mauvais pronostic chez les patients atteints de pneumonie à nouveau coronavirus. J Thromb Haemost. 2020 ; 18 (4) : 844–7.

[15]. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 et maladie thrombotique ou thromboembolique : implications pour la prévention, le traitement antithrombotique et le suivi. J Am Coll Cardiol. Avril 2020 ; S0735109720350087.

[16]. Luo W., Yu H., Gou J. Vol. 2020020407.2020. Pathologie clinique d'un patient critique atteint d'une nouvelle pneumonie à coronavirus (COVID-19).

[17]. Danzi G.B., Loffi M., Galeazzi G., Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur. Heart J. 2020 ;41(19) :1858.

[18]. Wichmann D., Sperhake J.P., Lutgehetmann M. Autopsy findings and venous thromboembolism in patients with COVID-19 : a prospective cohort study. Ann. Intern. Med. 2020 doi: 10.7326/m20-2003.

[19]. Liu Q., Wang R.S., Qu G.Q. Gross examination report of a COVID-19 death autopsy. Fa yi xue za zhi. 2020;36:21–23.

[20]. Zhang T., Sun L.X., Feng R.E. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chin. J. Tuberc. Respir. Dis. 2020;43

[21]. Poissy J., Goutay J., Caplan M. Embolie pulmonaire chez les patients COVID-19: prise de conscience d'une prévalence accrue. Circulation. 2020.120.047430.

[22]. Oxley TJ, Mocco J., Majidi S. Accident vasculaire cérébral de gros vaisseau comme une caractéristique de présentation de Covid-19 chez les jeunes. N. Engl. J. Med. 2020; 382.

[23]. Mao L., Jin H., Wang M. Manifestations neurologiques de patients hospitalisés atteints d'une maladie à coronavirus 2019 à Wuhan, Chine. JAMA Neurol. 2020 / jamaneurol.2020.1127.

[24]. Lodigiani C., Iapichino G., Carenzo L. Complications thromboemboliques veineuses et artérielles chez les patients COVID-19 admis dans un hôpital universitaire de Milan, Italie. Thromb. Res. 2020; 191 : 9–14.

[25]. Klok FA, Kruip M., van der Meer NJM Incidence des complications thrombotiques chez les patients en soins intensifs gravement malades atteints de COVID-19. Thromb. Res. 2020 doi: 10.1016 / j.thromres.2020.04.013.

[26]. Klok FA, Kruip M., van der Meer NJM Confirmation de l'incidence cumulative élevée de complications thrombotiques chez les patients en soins intensifs atteints de COVID-19 : une analyse mise à jour. Thromb. Res. 2020 doi: 10.1016 / j.thromres.2020.04.041.

[28]. Helms J., Tacquard C., Severac F., Leonard-Lorant I., Ohana M., Delabranche X. Risque élevé de thrombose chez les patients atteints d'une infection sévère par le SRAS-CoV-2 : une étude de cohorte prospective multicentrique. Soins intensifs Med. 2020.

[29]. Thomas W., Varley J., Johnston A. Complications thrombotiques des patients admis aux soins intensifs avec COVID-19 dans un hôpital universitaire au Royaume-Uni. Thromb. Res. 2020 doi: 10.1016 / j.thromres.2020.04.028.

[30]. Levi M Scully M Comment je traite la coagulation intravasculaire disséminée. Du sang. 2018 ; 131 : 845-854.

[31]. Cui S, Chen S, Li X et al. Prévalence de la thromboembolie veineuse chez les patients atteints de pneumonie sévère à nouveau coronavirus. [Publié en ligne avant l'impression le 9 avril 20202]. J Thromb Haemost.

[32]. Tang N Bai H Chen X Gong J Couvercle Soleil Z Le traitement anticoagulant est associé à une diminution de la mortalité chez les patients atteints d'une maladie à coronavirus sévère 2019 atteints de coagulopathie. J Thromb Haemost. 2020 ;

[33]. Thachil J Wada H Gando S et coll. Guide provisoire de l'ISTH sur la reconnaissance et la prise en charge de la coagulopathie dans le COVID-19. J Thromb Haemost. 2020 ;

[34]. Zuily V. Dufrost D. Wahl Arch Mal :Thrombose artérielle et veineuse au cours du COVID-19 Arterial and venous thrombosis in patients with COVID-19 S. Coeur Vaiss Prat 2020;2020:16–19.

[35]. 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.

[36]. Hunt BJ, Levi M. Re The source of elevated plasma D-dimer levels in COVID-19 infection. Br J Haematol 2020;190(3).

[37]. Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. J Thromb Haemost 2020.

[38] Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection : a systematic review and meta-analysis. Lupus 2018 ;27:572–83.

[39]. Devreese KMJ, Linskens EA, Benoit D, Peperstraete H. Antiphospholipid antibodies in patients with COVID-19: a relevant observation? J Thromb Haemost 2020.14994.

[40]. Khider L, Soudet S, Laneelle D, Boge G, Bura-Rivière A, Constans J, et al. Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in outpatients with COVID-19. J Med Vasc 2020 ;45:210–3.

[41]. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 ;382(18):1708-1720. 2020.

[42]. Huang C.Wang Y. Li X et coll. Caractéristiques cliniques des patients infectés par le nouveau coronavirus 2019 à Wuhan, en Chine. Lancette. 2020 ; 395 : 497-506.

[43]. Léa Satre Buisson Coagulopathie associée au COVID-19 : les éléments essentiels pour l'anesthésiste-réanimateur Prat Anesth Reanim. 2020 Sep ; 24(4): 190–195.2020

[44]. Klok FA . Kruip M . van der Meer NJM et coll. Incidence des complications thrombotiques chez les patients en soins intensifs gravement malades atteints de COVID-19. Thromb Res. 2020 ;

[45]. Zhang, Y, Xiao, M, Zhang, S et al. Coagulopathie et anticorps antiphospholipides chez les patients atteints de COVID-19. N Engl J Med. 2020 ; 382 (17): e38.

[46]. Gralinski LE, Sheahan TP, Morrison TE, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. MBio. 2018 ;9(5).

[47]. Dosquet C, Weill D, Wautier JL. Cytokines and thrombosis. J Cardiovasc Pharmacol. 1995 ;25(suppl 2): S13-S19.

[48]. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China : a descriptive study. Lancet. 2020 ;395(10223): 507-513.

[49]. Tang N., Li D., Wang X., Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–847.

[50]. Paranjpe I., Fuster V., Lala A., Russak A., Glicksberg B.S., Levin M.A. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76:122–124.

[51]. Adam Flaczyk , Rachel P. Rosovsky , Clay T. Reed , Brittany K. Bankhead-Kendall , Edward A. Bittner , et Marvin G. Chang Comparison of published guidelines for the management of coagulopathy and thrombosis in critically ill patients with desired COVID 19: implications for clinical practice and future investigations. Crit Care . 2020; 24: 559.

[52]. Sophie Susen, Charles Ambroise Tacquard, Alexandre Godon, Alexandre Mansour,Garrigu, Philippe Nguyen, Anne Godier, Sophie Testa, Pierre Albaladejo, Yves Gruel, :Traitement anticoagulant pour la prevention du risque thrombotique chez un patient hospitalise avec covid-19 et surveillance de l'hemostase - Propositions du GIHP et du GFHT ;Version courte (3 avril 2020).

[53]. Needleman L., Cronan J.J., Lilly M.P., Merli G.J., Adhikar S., Hertzberg B.S. Multidisciplinary recommendations from the Society of Radiologists in Ultrasound Consensus Conference. Ultrasound for lower extremity deep venous thrombosis. Circulation. 2018 ;137 :1505–1515.

[54]. Bernardi E. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA. 2008 ;300(14) :1653–2165.