Acta Cardiologia Indonesiana

pISSN:2460-5700

ISSN:2579-4345

Web page: jurnal.ugm.ac.id/v3/jaci

Hypercoagulability State and Role of Anticoagulants in Corona Virus Disease 2019 (Covid-19)

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Keywords:
Coagulopathy associated Covid-19, hypercoagulability state, anticoagulants

Manuscript submitted: 21 Mart 2021
Revised and accepted: 20 April 2022

ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious viral disease caused by the severe acute respiratory syndrome coronavirus-2 or what is known as SARS-CoV-2. This virus is known to attack the respiratory tract, but recent studies showed that it is known to cause multiorgan damage causing morbidities and mortalites worldwide. Although the COVID-19 mortality rate is known to be related to lung organs damage, various studies have shown damage to the cardiovascular system, in the form of coagulopathy. The mechanism of coagulopathy in COVID-19 patients is not the same as the disease in general and it is still not known with certainty. However, recent studies have shown benefits of using anticoagulant therapy to COVID-19 patients. This review article aims to discuss the pathophysiology of coagulopathy in COVID-19 patients, the hypercoagulability state in COVID-19 patients and the role and management of anticoagulant therapy. Through this review article, it is hoped that the use of anticoagulants in COVID-19 patients can be understood and applied in the management of patients with COVID-19 to reduce morbidity and mortality in Indonesia.

INTISARI

Coronavirus Disease 2019 (COVID-19) adalah suatu penyakit infeksi yang disebabkan oleh virus severe acute respiratory syndrome coronavirus-2 atau yang dikenal dengan SARS-CoV-2. Virus ini diketahui menyerang saluran pernapasan, namun dewasa ini, virus ini diketahui juga dapat menyebabkan kerusakan multi-organ yang menyebabkan morbiditas dan mortalitas di seluruh dunia. Meskipun angka kematian COVID-19 diketahui berkaitan dengan kerusakan pada organ paru-paru, namun berbagai penelitian menunjukkan adanya kerusakan pada sistem kardiovaskular, berupa koagulopati. Mekanisme terjadinya koagulopati pada pasien COVID-19 tidak sama dengan penyakit pada umumnya dan hingga saat ini masih belum diketahui secara pasti. Namun berbagai penelitian menunjukkan adanya keuntungan pemberian terapi antikoagulan terhadap pasien COVID-19. Tinjauan pustaka ini bertujuan membahas patofisiologi koagulopati pada pasien COVID-19, status hiperkoagulabilitas pada pasien COVID-19 serta peran dan manajemen penggunaan terapi antikoagulan. Melalui tinjauan pustaka ini diharapkan penggunaan antikoagulan pada pasien COVID-19 dapat dipahami dan diterapkan dalam penanganan pasien dengan COVID-19 untuk menurunkan morbiditas dan mortalitas di Indonesia saat ini.

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious viral disease caused by the severe acute respiratory syndrome coronavirus-2 or what is known as SARS-CoV-2. This virus is known to attack the respiratory tract, but recent studies showed that it is known to cause multiorgan damage causing morbidities and mortalites worldwide.[1] In Indonesia, as of October 1, 2020, confirmed cases have reached 287,008 cases with 61,321 active cases and 10,740 cases died. Currently the cases are still increasing with the addition of cases ranging from 4000 cases per day.

COVID-19 has a wide spectrum of diseases, ranging from asymptomatic, mild symptoms, moderate symptoms, severe symptoms, and critical ones (Diaz et al., 2020). Although the COVID-19 mortality rate is known to be related to damage to the lung organs, various studies have shown that there is damage to the cardiovascular system, in the form of coagulopathy in COVID-19 patients.[2] Research shows that in

COVID-19 patients, there are signs of coagulopathy, such as found increased D-dimers, fibrin degradation product (FDP), mild thrombocytopenia, and prolonged prothrombin time leading to disseminated intravascular coagulation (DIC). Increased D-dimers are also known to correlate with the severity of COVID-19. The mechanism of coagulopathy in COVID-19 patients is not the same as the disease in general and it is still not known with certainty. However, various studies have shown the advantages of providing anticoagulant therapy to COVID-19 patients.[2,3] This review article aims to discuss the pathophysiology of coagulopathy in COVID-19 patients, the hypercoagulability state in COVID-19 patients and the role and management of anticoagulant therapy. Through this review article, it is hoped that the use of anticoagulants in COVID-19 patients can be understood and applied in the management of patients with COVID-19 to reduce morbidity and mortality in Indonesia

Discussion

1. The pathopgysiology of coagulopathy in COVID-19

Coagulopathy is defined as a disorder of the coagulation/clotting system which can then manifest as a blood clot (thrombus) either in the arteries, veins or as a whole (systemic). The pathophysiology of coagulopathy in COVID-19 is known to be different from coagulopathy in general. SARS-CoV-2 causes coagulopathy, one of which is through the relationship between thrombosis and inflammation. In COVID-19 inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase, ferritin, interleukin-6 (IL-6) and D-dimer have increased, where IL-6 and fibrinogen are correlated with each other.[3] Inflammation and thrombosis that occurs in COVID-19 is known to originate in the alveoli and occurs through several mechanisms (Figure 1), which are described as follows:

a. Localized intravascular coagulopathy

In COVID-19 patients, thrombus formation generally occurs in the pulmonary blood vessels or what is called Pulmonary Intravascular Coagulopathy. This process can then systemically induce microthrombus to cause multi-organ failure. This is evidenced by the discovery of signs of endothelial dysfunction and thrombo-inflammation in the brain, kidneys, and several other organs in COVID-19 patients.[3] Immune response factors that promote PIC include, among others, widespread alveolar damage and inflammation, extensive interstitial inflammation and activation of pulmonary macrophages, dysregulation of the innate lung immune response, activation of innate immunity, and mechanical ventilation that forces viral immunostimulating molecules into the micro-vascular pathways. and cause immune-thrombosis1. This process can develop systemically into DIC, although some researchers believe that laboratory abnormalities that lead to DIC are a reflection of coagulopathy that occurs in pulmonary vessels due to severe inflammatory processes in the alveoli.[3]

b. Inflammatory cytokines

Increased inflammatory cytokines such as IL-6, IL-7, TNF, CCL2, CCL3, and soluble IL-2 receptors have been found in COVID-19 patients. This increase in cytokines is thought to contribute to the formation of thrombosis through several mechanisms, such as activation of monocytes, neutrophils, and endothelium which can lead to pro-thrombotic conditions.[3] Continuous PIC will stimulate excessive inflammatory processes resulting in hyperinflammation which is characterized by Cytokine Storm Syndrome (CSS) or Macrophage Activating Syndrome (MAS). Cytokines (IL-2, IL-6, TNF and others) stimulate coagulopathy and systemic thrombosis. This thrombotic cascade is typical and is known as immunothrombosis. This coagulation and thrombosis will result in Multi Organ Dysfunction (MOD) and Multi Organ Failure (MOF).[4]

c. Endothelial activation and endothelial dysfunction

Previous studies have shown that patients with COVID-19 have severe endothelial damage accompanied by the presence of intracellular viruses, thrombosis, and microangiopathy. In COVID-19 patients, endothelial activation can be seen from an increase in the expression of vonWillebrand Factor (vWF) and Factor VIII (FVIII). This increase could be due to inflammatory cytokines, complement activation, or a direct result of infection with the SARS-CoV-2 virus in endothelial cells that have angiotensin converting enzyme 2 (ACE2) receptors. Endothelial dysfunction and severe vasodilation in COVID-19 patients can also cause pulmonary shunting. This is exacerbated by the increased dead space in the alveoli due to microangiopathic thrombosis and embolism.[5]

d. Hypoxia

The coagulation system in the body is also affected by hypoxia. Hypoxia is known to induce platelet aggregation and activate the coagulation pathway, while in COVID-19, hypoxia is one of the main symptoms. The same is common in other diseases such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS).[5]

e. The role of mononuclear phagocytes (MNP)

Mononuclear phagocytes (MNP) are a group of cells that migrate when they receive certain molecular signals and function as phagocytes and play a role in the body's immune system. MNP cells include monocytes, macrophages, and dendrite cells. Based on previous reports, MNP was found in many COVID-19 patients with severe symptoms. Circulating monocytes found in COVID-19 patients are known to produce tumor necrosis factor a (TNFa) and IL-6 continuously. This is similar to what happened in MAS, where MNP cells including monocytes can support thrombosis, because activated monocytes can increase the production of tissue factor (TF) which can trigger the coagulation cascade.[3] In addition, MAS can also trigger TF expression in endothelial cells which contributes to the activation of the coagulation cascade.[1]

f. Neutrophil extracellular traps (NET)

Examination of COVID-19 patients showed an increase in NET which was previously known to have implications for the incidence of acute respiratory distress syndrome (ARDS) in influenza patients. Recent research has shown that activation of neutrophils and TEN causes a cytokine storm to occur and results in severe COVID-19 symptoms.[3]

g. Complement-mediated microangiopathy

Research shows that complement deposits are found in inflammatory thrombogenic vasculopathy in COVID-19 patients. In addition, the irregular activation of the complement system due to COVID-19 can also cause cytokine storms. This is generally mediated by the pro-inflammatory effects of anaphylacticins C3a and C5a.[3]

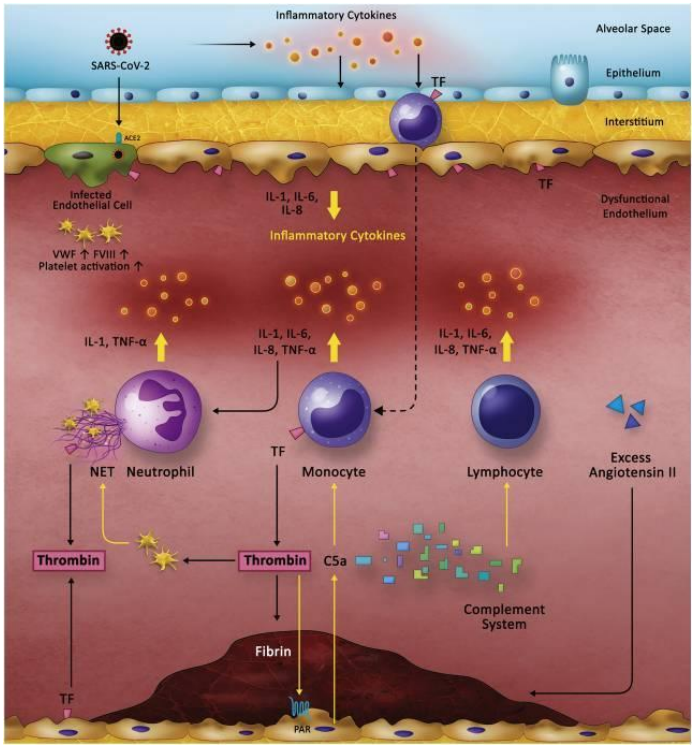

Figure 1. The pathopgysiology of coagulopathy in COVID-193

h. Renin-Angiotensin System (RAS) disregulasion

The RAS system is known to play an important role in COVID-19 because SARS-CoV-2 has a high affinity for the ACE2 receptor, which is structurally similar to the ACE receptor. ACE itself functions to activate angiotensin I (ANGI) and produce ANGII which will bind to angiotensin-type I receptors (AT1R) which will then cause vasoconstriction and increase blood pressure. ANGII has a function as a negative regulator of ACE2. When the SARS-CoV-2 virus binds to the ACE2 receptor, this will cause virus internalization and release of ACE2 which results in decreased ANGII degradation resulting in increased binding to AT1R and causing increased lung injury. ANGII binding with AT1R can also stimulate the release of IL-6 which also contributes to the occurrence of cytokine storms. In addition, in endothelial cells, AT1R activation by ANGII can also induce TF and the expression of inhibitor activator plasminogen 1 (PAI-1) which can cause Hypercoagulability state.[3]

2. Hypercoagulobility state in COVID-19

Previous Hypercoagulability state were also found in SARS-CoV-1 and MERS-CoV infections, where the two viruses often found thrombosis. In SARS-CoV-2 infection, venous and arterial thrombosis is also found.[3]

a. Venous thromboembolism

Pulmonary embolism (PE) is one of the most common forms in COVID-19 patients. Patients with older age, male gender, Caucasian ethnicity and African-American are said to have a higher risk for hypercoagulation.[3] Venous thrombus manifestations can be in the form of venous thromboembolism (VTE), either in the form of PE or deep vein thrombosis (DVT). This is evidenced by computed tomography pulmonary angiography (CTPA) data which found PE in 10 of 30 patients (33% of CTPA performed) and the incidence of VTE in 33% of 44 patients who underwent imaging studies within the first 24 hours of treatment. The characteristic feature of this condition is sub-segmental PE.[4]

b. Arterial thromboembolism

Although it is somewhat rarer than cases of venous thromboembolism, arterial thromboembolism is also often found, for example in the following conditions: (1) Myocardial infarction (MI), based on a study in Italy, the MI incidence rate reached 1.1% of all COVID-19 patients in the study. Troponin was significantly increased in the non-survivor group, so that the increase in troponin was considered to have prognostic value, although the increase in troponin could also be caused by renal injury or myocarditis[3]; (2) Stroke, is one of the complications of COVID-19 with an incidence rate of 4.2-5.9%. Cerebral venous sinus thrombosis (CVST) is one of stroke associated thrombosis due to coagulopathy in COVID-19 patients. There are several case reports regarding the incidence of CVST in COVID-19 patients with manifestations such as headache, decreased consciousness, neurological deficits, and seizures as evidenced by head computed tomography (CT) scan or CT Venogram.[4] In an American study, the incidence of ischemic stroke increased by 7 times in a group of patients aged <50 years in New York City.[3] (3) Microvaskular thrombosis, based on the autopsy report, in COVID-19 patients, evidence of thrombosis microangiopathy (TMA) was found in the lung organs. This microthrombus can be found in the lungs and even outside the lung organs, such as intestinal ischemia, lower extremity ischemia and cutaneous ischemia. This microthrombus can also be found in asymptomatic patients. Pathological examination revealed an infiltrate of inflammatory cells with fibrin deposits in the focal area, indicating a hypercoagulable condition in the lungs. Meanwhile, in kidney disorders, it is still unknown whether the disorders that occur in the kidneys are the result of viral toxicity or because of endothelial / microvascular damage to the kidneys.[3]

In the case of hypercoagulation, overcoming the underlying disease is a step in managing hypercoagulability state. However, in COVID-19, specific therapy to deal with COVID-19 has not yet been found, so avoiding the sequel to coagulopathy caused by COVID-19 is the main focus in the management of COVID-19 patients.[3]

Laboratory monitoring

The hypercoagulation that occurs in COVID-19 is a combination of both inflammatory reactions and thrombosis, so it is important to monitor the inflammatory response and the coagulation system activation. In patients with COVID-19, increased fibrinogen, fibrinogen degradation product (FDP), prothrombin time (PT), activated Partial Thromboplastin Time (aPTT), and shortening of thrombin time (TT) have been widely reported. Hematological parameters such as neutrophil count, lymphocyte, neutrophil/lymphocyte ratio, platelets and hemoglobin were also considered to be correlated with the prognosis of COVID-19. However, the parameter that comes closest to the prognostic value is the D-dimer.[3]

The D-dimer marker indicates the formation and physiological degradation processes of the activated coagulation cascade. In COVID-19, D-dimers represent the pathological activation of the hemostasis pathway. Just like in patients with DIC, COVID-19 patients show an increase in D-dimers, platelets, decreased fibrinogen and antithrombin, so serial monitoring of platelets, PT, aPTT, D-dimers and fibrinogen can be used as predictors of the recovery of COVID-19 patients3. In COVID-19 patients, an increase in D-dimer > 1 μg / mL is known to have a correlation with patient mortality.[2]

In the initial study in Wuhan, patients with COVID-19 showed a decrease in leukocytes or leucopenia. However, recent reports showed that in COVID-19 patients with severe symptoms who require an intensive care unit (ICU), there is an increase in neutrophils or neutrophilia. A decrease in the lymphocyte count is one parameter that has been consistently reported in COVID-19 patients. This decrease in lymphocyte count or lymphopenia is considered a marker of poor prognosis in the patient. This decrease in lymphocyte count is reported to have a positive correlation with mortality. One of the mechanisms underlying lymphopenia is direct infection of the SARS-CoV-2 virus against lymphocytes known to have ACE2 receptors. Although the proportion of lymphocytes with the ACE2 receptor is low, a retrospective study of COVID-19 patients with hypertension showed that patients treated with ACE inhibitors / angiotensin receptor blockers (ARBs) had cluster of differentiation 3+ (CD3 +) and CD8 + lymphocyte cell counts. which was higher than the group without therapy.[3]

Neutrophil Lymphocyte Ratio (NLR) is a prognostic predictor of septic shock, pancreatic cancer, and bacteremia because NLR is a sensitive marker in the early stages of inflammation and in conditions of physiological stress. Several reports suggest that an increase in NLR in COVID-19 patients correlates with disease severity. A decrease in platelets is not a characteristic feature of COVID-19, however, in some cases, a decrease in platelets is considered to indicate a poor prognosis. To date, it is unclear whether the platelet drop that occurs reflects the DIC process or is a direct consequence of infection with the virus in platelet cells. There are various mechanisms that are thought to trigger a decrease in platelets, such as the emergence of autoantibodies and immune complexes that affect platelet clearance, direct infection of hematopoietic stem cells / progenitor cells and megacaryocytes that cause decreased platelet production, and pathological activation of the coagulation pathway. In COVID-19 patients with severe symptoms, anemia is often found. However, the same symptoms were not found in patients who did not undergo invasive mechanical ventilation.[3]

Anticoagulants therapy

Although the pathophysiology of coagulopathy that occurs in COVID-19 patients is not certain, the management of hypercoagulation has been prepared using the relationship between inflammation and thrombosis as the basis for developing guidelines. One of them is the use of anticoagulant drugs either with prophylactic, intermediate or therapeutic doses, according to coagulation parameters and clinical conditions. Some of the recommendations used globally by various institutions and communities are summarized in Figure 2.[3]

Heparin has been involved in binding to the Covid-19 protein spike as well as lowering interleukin-6 (IL-6), which has been shown to increase in COVID-19 patients, and thus heparin or LMWH remains the best anticoagulant choice for hospitalized patients. It is possible that these patients may require continued anticoagulation for a certain time after discharge from the hospital.[2]

Fibrinolysis

In acute respiratory distress syndrome (ARDS), fibrin deposition in the alveoli and lung parenchyma causes worsening of ventilation. The administration of anticoagulants such as heparin can indeed prevent further fibrin deposition but cannot improve fibrin deposition that has been formed before, in contrast to the use of fibrinolysis which can improve fibrin deposition as a whole. However, giving fibrinolysis is known to cause complications in the form of bleeding. In a study conducted on patients with ARDS conditions, giving fibrinolysis in the form of streptokinase using a nebulizer device can increase oxygenation and lung movement compared to patients without a nebulizer, but there have not been the same studies on COVID-19 patients, so the use of fibrinolysis is still not recommended.[3]

Recommending source	When to consider prophylactic dose anticoagulation	When to consider therapeutic dose anticoagulation
International Society of Thrombosis & Hemostasis	In all patients with COVID-19 who are hospitalized, including non-critically ill, in the absence of contraindications (active bleeding and platelet count $< 25 \times 10^9$/L). PT and PTT abnormalities are not considered a contraindication [117].	
American Society of Hematology (Expert Panel)	All hospitalized patients with COVID-19. LMWH or fondaparinux (suggested over UFH to reduce contact) in the absence of increased bleeding risk[121].	• Intubated patients who develop sudden clinical and laboratory findings consistent with PE, especially when chest X-ray and/or markers of inflammation are stable or improving • Patients with physical findings consistent with thrombosis, such as superficial thrombophlebitis, peripheral ischemia or cyanosis, thrombosis of dialysis filters, tubing or catheters, or retiform purpura • Patients with respiratory failure, particularly when D-dimer and/or fibrinogen levels are very high, in whom other causes are not identified (e.g., ARDS, fluid overload) [122]
Thrombosis UK	• For CrCl > 30 mL/min: Give LMWH or fondaparinux • For CrCl < 30 mL/min or acute kidney injury: UFH 5000 units SC BD or TDS or dose-reduced LMWH • All completely immobilized patients would benefit from intermittent pneumatic compression in addition to pharmacological thromboprophylaxis • Mechanical thromboprophylaxis should be used alone if platelets $< 30 \times 10^9$/L or bleeding [123].	
National Institute for Public Health of the Netherlands	All patients with (suspected) COVID-19 admitted to the hospital, irrespective of risk scores.	• In patients with a D-dimer $< 1{,}000$ µg/L on admission but a significant increase during hospital stay to levels above 2,000-4,000 µg/L, when imaging is not feasible, therapeutic-dose LMWH can be considered when the risk of bleeding is acceptable. • In patients with a strongly increased D-dimer on admission (e.g. 2,000-4,000 µg/L), D-dimer testing should be repeated within 24-48 h to detect further increases in which case imaging for DVT or PE, or empiric anticoagulation, should be considered [15].

Figure 2. Current guidelines and recommendations on prophylactic and therapeutic anticoagulation from different societies and institutions

3. The role of anticoagulants in COVID-19

In a previous study, 31% of COVID-19 patients admitted to the ICU experienced venous and arterial thromboembolism following standard prophylactic doses. The prospective cohort study showed that 42% of COVID-19 patients with ARDS had thrombotic complications despite being given therapeutic or prophylactic doses of anticoagulants. This suggests the importance of empirically administered therapeutic anticoagulants. The incidence of embolism is found in patients with severe symptoms, but clinical symptoms and diagnosis of embolism are often difficult to establish, so empiric administration of anticoagulant therapy needs to be considered in COVID-19 conditions, although there is not much evidence to support it further. Heparin and heparin products are potential therapeutic options. The role of heparin in inhibiting thrombin has an influence on the inflammatory response. Heparin also has the ability to bind inflammatory cytokines, deactivate neutrophil chemotaxis, inhibit factor C5a complement, and inhibit acute phase proteins.[5]

In the management of anticoagulant administration, it is necessary to clearly define which patients will benefit from anticoagulant administration, the dose of anticoagulant therapy, duration of therapy, and monitoring of anticoagulant therapy. This is important to determine a clear algorithm or protocol for administering anticoagulants in COVID-19 cases.

Patient's criteria

The use of thrombotic prophylaxis is recommended especially in COVID-19 patients who are admitted to the ICU. A study in the Netherlands showed that most COVID-19 patients admitted to ICU experienced pulmonary embolism, arterial and venous thrombosis. Different studies recommend that anticoagulant therapy be given to patients with a D-dimer value four times the upper limit of normal, except in patients with contraindications. While the European Society of Cardiology provides anticoagulant therapy based on several criteria, such as dyspnea, respiratory rate> 24 times / minute, oxygen saturation <90%, increased C-reactive protein (CRP), increased D-dimers, and increased fibrinogen.[1,2]

The International Society of Thrombosis and Hemostasis (ISTH) introduced a scoring method to identify the incidence of DIC associated with sepsis or what is called sepsis-induced coagulopathy or SIC (Figure 3). In a study that applied the SIC score to patients with severe symptoms of COVID-19 found that there was a difference in mortality rates in patients with SIC scores ≥4 or an increase in D-dimer 6 times higher than the upper limit who received heparin therapy compared to those who received no therapy. This suggests that patients with high SIC or D-dimer scores can have a good prognosis with anticoagulant therapy.[1]

Item	Score	Range
Platelet count ($\times 10^9$/L)	1	100–150
	2	< 100
INR	1	1.2–1.4
	2	> 1.4
SOFA score	1	1
	2	≥ 2
Total score for SIC	≥ 4	

Abbreviations: *INR* international normalized ratio, *SOFA* sequential organ failure assessment

Figure 3. SIC score1

In Indonesia, based on IDI recommendations (2020), moderate COVID-19 patients who are hospitalized are included in the criteria for prophylactic anticoagulants. To assess the risk of bleeding, IDI recommends the use of the IMPROVE risk scoring (Figure 4). Meanwhile, in patients with mild symptoms, prophylactic anticoagulant administration is based on the results of the D-dimer examination.[4]

For patients with special conditions, such as complications of stroke, routine use of anticoagulants for other diseases, consultants should be consulted before administering anticoagulants. Meanwhile, for pregnancy and breastfeeding conditions, giving anticoagulants is not a contraindication. For pregnant women with moderate, severe, and critical COVID-19, LMWH prophylaxis or other regimens are recommended according to the procedure, dosage, and dose adjustments according to the general population, unless labor is expected to occur within 12 hours, then new administration is carried out 12 postpartum hours. For pregnant, childbirth, and breastfeeding women who are asymptomatic or with mild symptoms, thromboprophylaxis, either oral or intravenous, is not required.

Bleeding Risk Factors	Points
Moderate renal failure, GFR 30-59 vs ≥ 60 mL/min/m²	1
Male vs female	1
Age, 40-84 y vs < 40 y	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/CCU	2.5
Severe renal failure, GFR < 30 vs ≥ 60 mL/min/m²	2.5
Hepatic failure (INR > 1.5)	2.5
Age, ≥ 85 y vs < 40 y	3.5
Platelet count < 50 × 10^9 cells/L	4
Bleeding in 3 mo before admission	4
Active gastroduodenal ulcer	4.5

Figure 4. IMPROVE bleeding risk[6]

Anticoagulants dose

The optimal dose of anticoagulant administration in COVID-19 is not clear, however, various reports have shown the benefits of administering anticoagulants, including the administration of heparin in prophylactic doses.[3] The main recommended prophylactic anticoagulants are low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Based on IDI recommendations (2020), for moderate symptomatic COVID-19 patients who are hospitalized, the standard dose of LMWH 40 mg is given subcutaneously 1 time a day for adults, while for children the dose is 1 mg / kgBB / 12 hours and administered subcutaneously. If there is kidney disease or obesity in adult patients, the dosage will be adjusted accordingly. The same is true for pediatric patients, if there is impaired renal function / shock (creatinine clearance <50ml / min / m2), the dose must be adjusted by the pediatric nephrologist consultant. For UFH, it can be given as a standard dose of 5000 units subcutaneously 2 times a day. Meanwhile, for critical patients who need ICU care with a platelet count of more than 25,000, anticoagulants are given more aggressively. Table 6 describes the use of anticoagulants in critically ill patients.[4]

A study in China recommended the use of high doses of heparin LMWH 100 IU/kg b.i.d for 3-5 days in patients with D-dimers four times the upper limit of normal, because the use of prophylactic doses of anticoagulants showed ineffective results in cases of COVID. -19 heavy. The high increase in fibrinogen in COVID-19 patients with severe symptoms can cause heparin irritation.[5] Meanwhile, the European Society of Cardiology recommends the use of enoxaparin 1 mg/kg SC b.i.d in non-ICU patients, and the use of the heparin drip protocol with close monitoring with aPTT target range of 60-85 seconds. If there are no signs of venous thrombosis, then the enoxaparin dose is reduced to 40 mg b.i.d, as shown in Figure 5.[1,2]

Drugs	Prophylaxis	Treatment
Enoxaparin	40 mg/24 hour SC in BMI >40 kg/m²: 40 mg/12 hour SC	1 mg/kgBW/12 hour SC or 1.5 mg/kgBW/24 hour SC
Nadroparin	2850 IU/24 hour SC	86 IU/kgBW/12 hour SC or 171 IU/kgBW/24 hour SC
Fondaparinux	2.5 mg/24 hour SC	BW <50 kg: 5 mg/24 hour BW 50-100 kg: 7.5 mg/24 hour BW >100 kg: 10 mg/24 hour SC
Unfractionated heparin (if GFR <30 mL/min or AKI)	5000 IU/12 hour SC or in obese patients: 5000 IU/8 hour SC	80 IU/kgBW given IV bolus followed with 18 IU/kgBW/hour IV continuous with normogram

AKI: acute kidney injury, BMI: body mass index, BW: body weight, GFR: glomerular filtration rate, IV: intravenous, SC: subcutaneous.

Figure 5. Anticoagulants doses for prophylaxis and treatment[7]

Anticoagulants duration

The duration of prophylactic anticoagulant administration in COVID-19 patients is during the patient's hospitalization. Prophylactic anticoagulants can be stopped if the patient's condition improves, can be actively mobilized and there is no high risk of thrombosis. In pregnant women, thromboprophylaxis is continued after delivery for up to 10 days after discharge. If sequela and morbidity are found, the administration can be extended up to 6 weeks after delivery. For thromboprophylaxis given after hospital discharge, it is necessary to consider using direct oral anticoagulant (DOAC).[4] The use of DOAC such as aspirin needs to be considered in COVID-19 patients who are no longer hospitalized.

In patients on long-term use of LMWH thromboprophylaxis, the IMPROVE criteria should be used. In patients treated with an IMPROVE score> 3, there is an increase in D-dimer 2 times the upper limit of normal, accompanied by 2 or more of the following criteria: age> 60, have a history of venous thromboembolism, thrombophilia, have a history of cancer, then administration of thromboprophylaxis needs to be extended. up to 39-45 days after discharge from hospital, either using a prophylactic dose of LMWH or with rivaroxaban. Meanwhile, in patients who have a history of using anticoagulants due to previous conditions, the use of anticoagulants needs to be extended up to 3 months.[3] Meanwhile, the use of high doses of LMWH is only recommended for 3-5 days.[1]

Patients on therapeutic anticoagulants, according to the Anticoagulation Forum (ACF) guidelines, the American College of Chest Physicians (ACCP), and the Scientific and Standardization Committee of ISTH (SCC-ISTH) recommend a minimum duration of anticoagulation of 3 months.[8]

Monitoring

Monitoring the platelet count, PT, aPTT, D-dimer, and fibrinogen in hospitalized patients should be recommended. Because several parameters, especially D-dimers, can help predict disease progression. For patients on heparin products, anti-Xa monitoring is recommended over aPTT.[3] There is no need for routine laboratory examinations when administering prophylactic anticoagulants, unless there are side effects such as bleeding, worsening that leads to DIC, or there are certain clinical conditions. Side effects to watch out for are bleeding and other complications.[9]

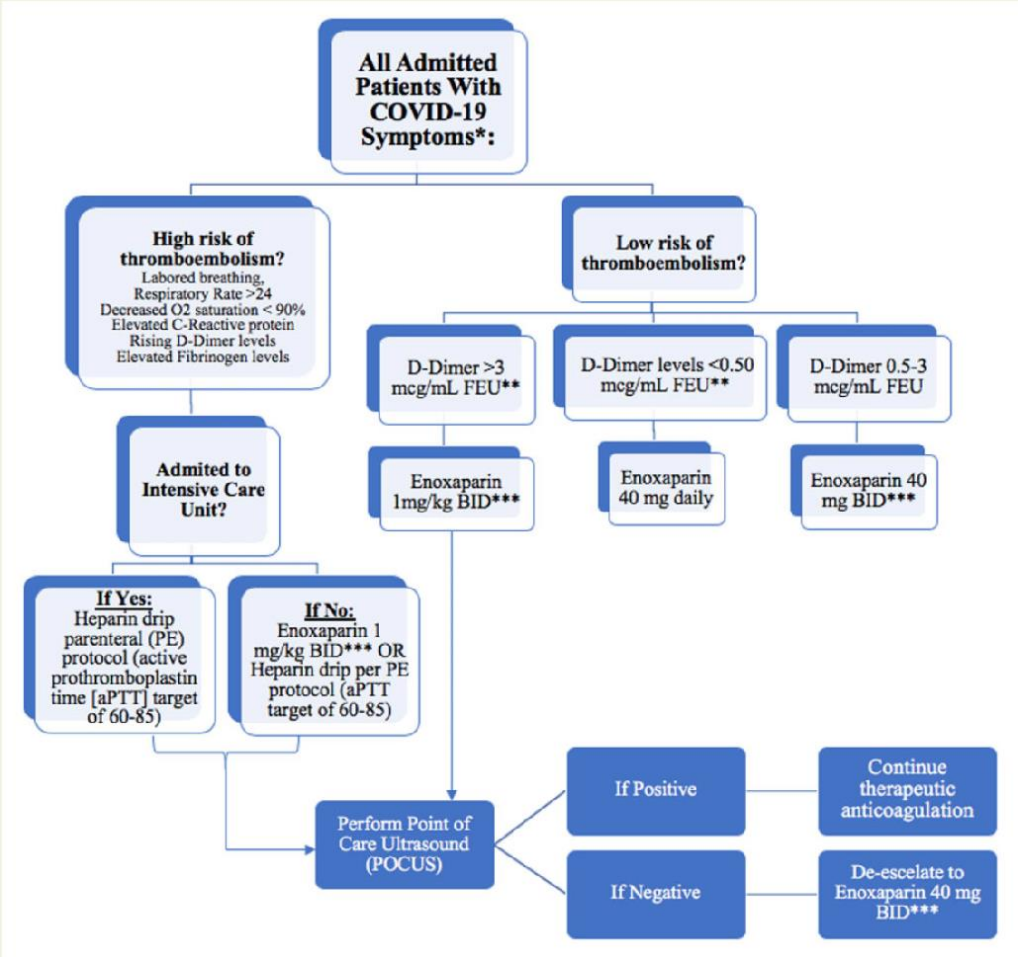

Figure 6. Algorhytm for using anticoagulants in COVID-19[2]

In addition, drugs that cause interactions with anticoagulant drugs should also receive special attention. A study shows that antiviral drugs interact with DOAC due to metabolites and competition against the CYP450 enzyme, giving rise to increased levels of DOAC in plasma. Some antiviral drugs the effect of anticoagulant drugs can increase due to their interaction with drugs such as atazanavir, lopinavir/ritonavir, and hydroxychloroquine, while tocilizumab can decrease the effect of anticoagulant drugs, while atazanavir, lopinavir/ritonavir, remdesivir, hydroxychloroquine, tocilizumab beta each had no effect on heparin products, such as fondaparinux and argatroban.[3,5]

4. Anticoagulants as prophylactic treatment in COVID-19

In each patient treated with COVID-19, an assessment is carried out whether thromboprophylaxis is needed and there are no contra indications for anticoagulant administration. Prophylactic anticoagulants are administered while the patient is being treated. Some of the existing guidelines contain debate about the criteria for a patient population that should receive pharmacological intervention, either full dose or standard prophylaxis. The ISTH guidelines recommend prophylaxis with LMWH for all COVID-19 patients unless contraindicated (PLT <25,000, or the presence of active bleeding). The ISTH guideline also provides a flow chart for assessing COVID-19 patient acceptance which basically shows the use of prophylactic LMWH only for patients with elevated D-dimer.[10]

The American College of Chest Physicians (CHEST) issued a recommendation in September 2020 that in acute and critical inpatients with COVID-19, it is recommended that anticoagulant thromboprophylaxis using LMWH or fondaparinux rather than anticoagulant thrombo-prophylaxis with UFH. CHEST also recommends anticoagulant thrombo-prophylaxis with LMWH, fondaparinux or UFH over anticoagulant thromboprophylaxis with DOAC.[11]

The pharmacological doses needed to reduce thrombosis in Covid-19 patients have not been well established. Studies and consensus statements show inconsistencies. It states that the recommended prophylactic dose of enoxaparin is a minimum dose of 40 mg/day to 0.5 mg/kg every 12 hours, a maximum dose of 80 mg/day. In patients with impaired renal function, a subcutaneous administration of 5000 units of heparin every 8 hours may be considered, or using a weight-appropriate dose of 70 units/kgBW.[10]

A few of studies also adding nebulized anticoagulant as a management patient in COVID-19. Nebulised UFH features a robust scientific and biological principle, and warrants pressing investigation of its therapeutic potential for COVID-19. Nebulised UFH as an anticoagulant act to limit fibrin deposition and microvascular thrombosis. Trials in acute lung injury patients found inhaled UFH reduced pulmonary dead space, coagulation activation, microvascular thrombosis, and clinical deterioration, resulting in chance not to use ventilator. Additionally, UFH has anti-inflammatory, mucolytic and anti-viral properties and, specifically, has been shown to inactivate the SARS-CoV-2 virus, thereby inhibiting pulmonary infection by SARS-CoV-2. Clinical studies have shown that inhaled UFH improves outcomes in other inflammatory respiratory diseases and acts as an effective mucolytic in sputum-producing respiratory patients.[12] A recent randomized controlled trial conducted in Australia suggests faster recovery of lung function, and the finding that fewer patients at risk for ARDS actually developed ARDS suggests a prophylactic effect of nebulised heparin.[13] UFH is widely available and cost effective, which may make this treatment also accessible for low- and middle-income countries,[12] such as here in Indonesia.

With each administration of anticoagulants, it is advisable to monitor coagulation parameters, including D-dimers. While giving enoxaparin to patients with weight gain obesity, mild / moderate renal dysfunction, or the elderly (> 65 years), monitoring of anti-Xa factor should be carried out.[10] However, in the guidebook for the management of Covid19 in Indonesia edition 3, it is stated that during the administration of anticoagulants, routine hemostasis laboratory tests are not required unless there are side effects of bleeding or worsening of DIC or other special clinical considerations.[4]

Bleeding side effects or other complications should be monitored during anticoagulant administration. If the patient's condition improves and the patient could do mobilization then do the reassessment. If the reassessment does not get a high risk of thrombosis, prophylactic anticoagulants can be stopped. Unless in certain patients with a risk of thrombosis, prophylactic anticoagulants can be continued after outpatient treatment.[4]

5. Thrombolysis as a management patient with pulmonary embolism

Systemic thrombolysis is administered to achieve rapid clot resolution and restoration of pulmonary perfusion thereby improving ventilation/perfusion suitability, and most importantly reducing RV afterload, reducing pulmonary vascular resistance, and thereby improving hemodynamics.[14] Thrombolytic therapy provides faster improvement in patients with PE, compared to UFH alone; this improvement is accompanied by decreased RV dilatation on echocardiography. The greatest benefit is seen when treatment is started within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6-14 days. A reported 8% of high-risk PE cases were unsuccessful thrombolysis, as assessed for persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 hours.[15]

A meta-analysis of thrombolysis trials in patients at high risk of PE, in the presence of mainly clinical cardiogenic shock, showed a significant reduction in the combined outcome of mortality and recurrent PE. This was achieved with a bleeding rate of 9.9% and an intracranial hemorrhage of 1.7%.[15]

Systemic thrombolysis therapy given to high-risk PE patients has a level of evidence of IB at the 2019 ESC recommendation. Whereas systemic thrombolysis therapy is not recommended in low or moderate risk PE (IIIC)

patients. Dosage and thrombolytic options are summarized in Figure 9 below. In patients at high risk of PE, it is necessary to consider the maximum dose of systemic thrombolysis, while the dose should be adjusted in patients with high risk of PE with relative contraindications.[15]

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute**
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]	History of haemorrhagic stroke or stroke of unknown origin
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Ischaemic stroke in previous 6 months
	Accelerated regimen: 1.5 million IU over 2 h	Central nervous system neoplasm
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 3 million IU over 2 h	Bleeding diathesis
		Active bleeding
		Relative
		Transient ischaemic attack in previous 6 months
		Oral anticoagulation
		Pregnancy or first post-partum week
		Non-compressible puncture sites
		Traumatic resuscitation
		Refractory hypertension (systolic BP >180 mmHg)
		Advanced liver disease
		Infective endocarditis
		Active peptic ulcer

Figure 7. Doses, regimens, and contraindication of thrombolysis [15]

Conclusion

COVID-19 has a wide spectrum of diseases, ranging from asymptomatic, mild symptoms, moderate symptoms, severe symptoms to critical. Coagulopathy is one of the manifestations often reported in COVID-19 patients. Hypercoagulability state can cause manifestations in the form of pulmonary embolism, DVT, myocardial infarction, stroke, and microvascular thrombosis. The pathophysiology of coagulopathy in COVID-19 is not the same as coagulopathy in general where the mechanism is still not clear, but it is suspected through several mechanisms involving thrombosis and inflammation such as localized intravascular coagulopathy, excessive expression of inflammatory cytokines, activation and endothelial dysfunction, hypoxia, role immune cells such as MNP, NET, complement to RAS system dysregulation.

In the principle's management of COVID-19, the main focus in hypercoagulation management is to avoid sequelae and comorbidities due to hypercoagulation. This can be done starting with monitoring of laboratory parameters, especially D-dimers. Prophylactic anticoagulant therapy is also recommended for COVID-19 patients, especially those who are hospitalized, including those treated in the ICU and non-ICU. The dosage and duration of anticoagulant administration can be adjusted according to the condition of each patient. Aggressive use of anticoagulants at therapeutic doses is recommended in patients with severe symptoms or patients admitted to the ICU. Monitoring of bleeding effects and drug interactions must be carried out carefully when administering anticoagulants so that maximum results can be obtained. Previous studies have reported the positive benefits of anticoagulant administration on the course of the disease and survival of COVID-19 patients. In the future, the use of anticoagulants with appropriate recommendations in Indonesia is expected to reduce the morbidity and mortality of COVID-19.

Acknowledgement

This review article would not have been possible without the exceptional support of my supervisors, Prof. Budi Yuli Setianto and Doctor Putrika Prastuti Ratna Gharini. Their enthusiasm, knowledge and exacting attention to detail have been an inspiration and kept my work on track. The authors have no conflicting financial interests.

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