East African Medical Journal Vol. 97 No. 11 November 2020
THE MECHANISM AND THE MANAGEMENT STRATEGY OF COVID-19 ASSOCIATED THROMBOEMBOLIC MANIFESTATIONS
Nazmul Hosain, Head of the Department of Cardiac Surgery, Chittagong Medical College & Hospital, Chattogram, Bangladesh. Abdul Momen Asif Rahim, Assistant Professor, Department of Cardiac Surgery, Level 3, Cardiac Surgery Building, Chittagong Medical College & Hospital, Chattogram, Bangladesh. Abu Kalam Mohammad Monwarul Islam, Associate Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, NICVD Building South Block, Dhaka, Bangladesh.

Corresponding author: Nazmul Hosain, Preferred Degree: MS (Cardiovascular & Thoracic Surgery), FACS. Affiliation: Chittagong Medical College & Hospital, Chittagong, Bangladesh, Address 66/5, West Rajabazar, Indira Road, Dhaka-1215, Bangladesh. Email: heartsurgeon007@gmail.com.

THE MECHANISM AND THE MANAGEMENT STRATEGY OF COVID-19 ASSOCIATED THROMBOEMBOLIC MANIFESTATIONS

N. Hosain, A. M. A. Rahim and A. K. M. M. Islam

ABSTRACT

Objectives: **Severe acute respiratory syndrome corona virus 2 (SARS-COV-2) is a recently known zoonotic coronavirus that has devastated the whole world. The objective of this review paper is to find out the available information related to COVID-19 infection and thromboembolism. This would help build better understanding of the pathophysiology and effective management strategy of thromboembolism in COVID-19 patients.**

Data sources: **A few articles are available on printed versions, but many more are available online versions or in the pipeline. We used various search engines to find out COVID-19 and thromboembolism related articles.**

Study selection: **The papers depicting various aspects of COVID-19 and thromboembolism have been selected and analyzed. Their core messages have been extracted and compiled.**

Data extraction: Data have been collected from the articles available from MEDLINE and Google Scholar up to July, 2020. We also gathered information from doctors involved in the treatment of the COVID patients.

Data synthesis: **Information on relationship between COVID-19 and thromboembolism has been collected. In addition, there have been reports of many sudden deaths attributed to deadly cardiac arrythmia and increased thromboembolic manifestation. A higher risk of vessel thrombosis has been correlated with severity of the disease and multiorgan involvement.**

Conclusions: **COVID-19 appears to be associated with thrombosis in general, both venous and arterial. These patients have increased risk of thromboembolism due to infection related inflammation, immobility and hypercoagulable state.**

Adequate thromboprophylaxis should be administered in all moderate to severe COVID-19 patients including patients of comorbidity and aged patients.

INTRODUCTION

Severe acute respiratory syndrome corona virus 2 (SARS-COV-2) is a recently known coronavirus that has acquired the ability of human to human transmission. The human infection of this apparently previous zoonotic virus is designated as COVID-19 by World Health Organization (WHO). During the last ten months, this virus has devastated the whole world. As of 17th November 2020, the total number of COVID-19 affected worldwide is 5,54,46,786 and total number of death is 13,34,596[1]. The actual numbers may be much higher as there seem to be the policy of denial by many countries. Moreover, due to lack of diagnostic facilities, many cases remain undetected. There have also been reports of many sudden deaths related to cardiac, cerebrovascular or pulmonary vascular events. These deaths may be attributed to deadly cardiac arrythmia and increased thromboembolic manifestation because of known and unknown SARS COV-2 infections. A higher risk of vessel thrombosis has been correlated with severity of the disease and multiorgan involvement[2]. The proposed mechanisms for COVID-19 induced thrombosis include a disease specific hypercoagulable state, cytokine-mediated diffuse microvascular damage, and, in some cases, reactive thrombocytosis[3].

The basic structure of SARS-COV-2 is quite like SARS and Middle East respiratory syndrome (MERS) viruses in Coronaviridae family, with its positive single stranded RNA genome containing a surface glycoprotein that studs the viral envelope, giving it the characteristic corona on electron microscope imaging[4]. These peplomers are known as spike proteins or S proteins and are thought to be responsible for the tropism displayed only with specific receptors on the cell surfaces of target organisms. SARS-COV-2 appears to preferentially target respiratory epithelium where it enters the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor similar to SARS-COV[5].

COVID-19 appears to be associated with thrombosis in general, both venous and arterial. This is observed by klok et.al.[6], who found that despite thromboprophylaxis of patients, venous thrombosis developed. Pulmonary embolism (PE) was found the most common and instances of arterial thrombosis including ischemic stroke were also noted. There are several ways in which COVID-19 pandemic may affect the prevention and management of thrombotic and thromboembolic disease[7]. These include the direct effect of COVID-19 or the indirect effects of infection. Through severe illness, stasis, immobility and hypoxia may predispose patients to thrombotic effect. Preliminary reports suggest that hemostatic abnormalities, including disseminated intravascular coagulation (DIC) occur in patients affected by COVID-19. Additionally, the severe inflammatory response, critical illness and underlying traditional risk factors may all predispose to thrombotic events. Investigational therapies for treating COVID-19 may have adverse drug interactions with antiplatelet agents and anticoagulants. Moreover, resource allocations or social distancing recommendation due to the pandemic may adversely affect the care of the patients even without COVID-19 presenting

with thrombotic events. For example (mis) perception that antithrombotic agents confer increased risk of contracting COVID-19 may lead to untoward interruption of anticoagulation by some patients[7].

METHODOLOGY

SARS COV-2 is a recently known virus, many of its characteristics and activities are yet to be found out. Research activities are being carried out about this virus in an unprecedented way in human history. A few articles are available on printed versions, but many more are available online versions or in the pipeline. We used various search engines to find out COVID-19 and thromboembolism related articles. Data have been collected from the articles available in MEDLINE and Google Scholar up to July, 2020. We also gathered information from doctors involved in the treatment of the COVID patients. Information on relationship between COVID-19 and thromboembolism has been collected and compiled.

The objective of this review paper is to find out the available information related to COVID-19 infection and thromboembolism. For obvious reason, very little material on this topic is readily available. Collection and compilation of information from various sources would help build better understanding of the pathophysiology of thromboembolism in COVID patients. This would be useful for the physicians engaged in the treatment of patients suffering from this dreadful disease. Most of the sudden and unexpected deaths of diagnosed and undiagnosed SARS COV-2 virus infected patients are attributed to thromboembolism. A clear understanding of the etiology, pathogenesis and management is thus important for proper treatment of this notorious disease.

Thrombosis in the context of COVID-19

Many critically ill patients with SARS-COV-2 are shown to have elevated levels of D-dimer, fibrinogen and fibrin degradation products compared to healthy controls[8]. This may be due to endothelial injury resulting in thrombin generation and fibrinolysis shut down, contributing to a hypercoagulable state. A similar relationship between acute respiratory distress syndrome (which can occur in patients with COVID-19) and deep vein thrombosis (DVT) has previously shown in influenza A (H1N1). The inflammatory disease process prolonged hospital stay and pre-existing comorbidities can contribute to venous thromboembolism (VTE). COVID-19 related risk factors for VTE therefore include age, male sex, obesity, cancer, comorbidities along with ICU admission, lung injury, cytokine storm and inflammation[8].

SARS-COV-2 is thought to gain entry to cells by binding to ACE2 receptors and the spike protein plays a vital role in this. This protein is cleaved by plasmin which is found to be higher in individuals with cardiovascular disease thus potentially making them more susceptible to poorer outcomes. The interaction of SARS-COV-2 with ACE2 receptor may cause endothelial damage as five-fold rise of von Willebrand factor levels has been reported in COVID-19 patients. It is well known that endothelial dysfunction is a component of Virchow's trait driving the development of thrombosis[7]. Angiotensin-converting enzyme 2 highly expressed in lung alveolar cells, cardiac myocytes, the vascular endothelium and other cells[8].

COVID-19 and hemostasis parameters

The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia, lymphopenia, monocytosis along with increased D-dimers and Serum Ferritin levels. Disease severity is variably associated with prolongation of the prothrombin time, (PT) international normalized ratio (INR) and thrombin time (TT) and variably by a trend towards shortened activated partial thromboplastin time (aPTT). Recently a study done by Tang et al. assessed 183 patients with COVID-19, among whom 21 (11.5%) had died. The notable differences between patients who died and those who survived were increased D-dimer and fibrin degradation products and PT prolongation by 14% ($p<0.001$). Furthermore, 71% of the COVID-19 patients who died fulfilled the international society on Thrombosis and Hemostasis (ISTH) criteria for DIC compared with only 0.6% among survivors. collectively these hemostatic changes indicate some form of coagulopathy that may predispose to thrombotic events although the cause is uncertain[9].

Nevertheless it is yet unknown whether these hemostatic changes are a specific effect of SARS-COV-2 or consequence of cytokine storm that precipitate the onset of SIRS as observed in other viral diseases. Another consideration that has not been investigated is the hemostatic changes seen with COVID-19 infection related to liver dysfunction. A recent study reported 3 cases with severe COVID-19 and cerebral infarction with associated bilateral limb ischemia, in setting of elevated antiphospholipid antibodies. Whether antiphospholipid antibodies play a major role in pathophysiology of thrombosis associated with COVID-19 requires further investigation[8].

COVID-19, Markers of myocardial injury and thrombotic disease

Elevated troponin levels are associated with poor outcomes in several studies of COVID-19. It should be remembered that troponin in COVID-19 patients may be elevated for various reasons. These include nonspecific myocardial injury, impaired renal function (leading to troponin accumulation), myocarditis, pulmonary embolism (PE) and myocardial infarction. Although anecdotal cases of COVID-19 patients presenting with ACS due to plaque rupture has been described, currently no such definite case have been published[8]. Myocardial injury can also occur through various mechanism in COVID-19 patients especially in those with preexisting cardiovascular disease. Systemic inflammation as well as shear stress due to increased coronary blood flow can result in plaque rupture thus causing myocardial infraction. A study showed that acute cardiac injury is more common with raised troponin I as well as significant ST elevation, which could mimic acute coronary occlusion. In patients with COVID-19 there is a higher prevalence of myocardial injury particularly in patients admitted to the ICU[7]. COVID-19 patients with preexisting cerebrovascular disease may be at a higher risk of developing strokes. Although there have not been many studies linking stroke and COVID-19, a study with 214 patients identified 5.7% of their patients with severe disease (n=88) to have developed a stroke of which four were ischemic[7].

Autopsy and Pulmonary Embolism

Complete autopsy studies were almost nonexistent in the initial phases of the outbreak; reasonably so, due to concerns related to infectivity, transmission rates, uncertainty and biosafety[10]. The few reports initially published were limited to postmortem biopsies in COVID-19 positive

patients or from lobectomy specimens initially resected for lung adenocarcinoma, but patients were later found to be COVID-19 positive. Pathologic features of exudative and proliferative phases of diffuse alveolar damage (DAD) were noted in these initial reports and overlapping features with SARS were also noted. Later complete autopsies performed in United States further supported the presence of DAD. Wichmann[11] and colleagues reported the findings of 12 consecutive, legally mandated autopsies of patients with COVID-19. The authors noted a high incidence of pulmonary embolism with or without underlying deep venous thrombosis, despite the absence of history of VTE. Massive pulmonary embolism was the cause of death in one third of the cases, with an additional one fourth with recent deep venous thrombosis but without pulmonary embolism. Seventy-five percent were men and two thirds of these were noted to have recent thrombosis in prostatic venous plexus. Preexisting coronary heart disease (50%), respiratory tract, obesity, and type 2 diabetes mellitus were noted but an absence of antemortem VTEs. Histologically exudative phase DAD was noted in two thirds and presence of pulmonary thrombi in 5 out of 8 cases with DAD. Similar histologic findings of DAD with microthrombi in 45% cases were also recently reported by Menter and associates in a series of 21 COVID-19–positive autopsies, 4 with prominent central pulmonary embolism.

Lax et al.[12] reported the findings of autopsies performed on 11 patients randomly selected among 48 hospitalized COVID-19–positive decedents. Significant preexisting comorbid conditions included hypertension, type 2 diabetes mellitus, obesity, chronic obstructive pulmonary disease, coronary heart disease, cancer, as well as history of cerebrovascular disease and pulmonary embolism. After autopsy tissue fixation, grossly visible pulmonary thrombi were noted in all cases with associated infarcts in 9 out of these 11 (81%) autopsies. During their hospital stay, 10 of the 11 deceased patients had received prophylactic dose anticoagulant therapy, with 2 receiving this therapy even before admission; thus suggesting that pulmonary thrombi were formed despite anticoagulant therapy. Apart from DAD, histologic evaluation highlighted the presence of multiple thrombi in small to mid-sized pulmonary arteries with adjacent lung parenchymal infarcts. These autopsy studies highlight the importance of thromboembolic events in COVID-19. Wichmann and colleagues highlighted the high incidence of pulmonary embolism with or without deep venous thrombosis, as well as presence of recent thrombi in prostatic venous plexus, in patients with no history of VTE, suggesting de novo coagulopathy in these patients with COVID-19.

Microvascular thrombi can be seen in DAD with various causes, including sepsis, trauma, viral, bacterial or mycoplasma pneumonia, aspiration, as well as toxic inhalation. Thus, microvascular thrombosis is not a distinctive or diagnostic feature of lung parenchymal involvement in patients with COVID-19. Ultrastructural evidence of acute endothelial injury has also been demonstrated, regardless of and without correlation with the cause of ARDS. Macrothrombi (thrombi in arteries with internal diameter >1 mm), large microthrombi, and capillary microthrombi have also been reported in patients with ARDS, due to other causes listed above. Pulmonary infarcts are also seen in patients with ARDS who died sooner (10 to 19 days) and later (≥20 days) after intubation[10]. Taken together, prior reports and more recent

descriptions of DAD in COVID-19 suggest that these microscopic findings are not specific to the etiology, but rather a general feature of acute lung injury at various stages of response to the injury.

The contributions of pulmonary thrombosis, embolism, or their combination to deaths of patients with COVID-19 may remain unaddressed because of the limited number of autopsy studies available. To address these questions more thoroughly it will require tissues obtained either as postmortem biopsies or as complete autopsies. Further, appropriately stored tissues may be used in future studies to assess not only the underlying pathogenesis but also to inform the development of diagnostic biomarkers and clinical trials of therapeutic strategies aiming to better equip us for the next pathogen, epidemic, or even pandemic[10].

Thrombosis and Clinical presentation

In a study including 30 intensive care unit (ICU) patients, 16 were found to have clinical DVT. The thrombus was found commonly in the femero-popliteal region (55%) followed by brachial-axillary veins. For upper limb involvement the authors proposed that continuous positive airway pressure ventilators can often be tied in a way that compress superficial or deep vessels of upper limbs leading to increased risk of DVT. Zhou et al. reported a case with concomitant lower limb venous and arterial thrombosis developed in a COVID-19 patient on the third day of admission. This illustrates the aggressive thrombotic burden in COVID-19 patients[13].

The Padua prediction score, which takes into consideration multiple factors can be used to assess patients for VTE. A score of >4 makes thromboprophylaxis necessary. It is evident that PE in the context of COVID-19 is complex and can present with no other risk factors. Furthermore, this is complicated because of the overlap with other respiratory symptoms and adds another layer of diagnostic challenge. A study evaluating outcome of 183 patients showed that 71.4% of non-survivors met the criteria of disseminated intra vascular coagulation (DIC)[7]. In DIC there can be simultaneous derangement of hemostasis and hypercoagulability resulting in abnormal coagulation profile. These patients showed elevated D-dimer levels, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and thrombocytopenia. Patients with COVID-19 may develop sepsis resulting in DIC. Sepsis induced coagulopathy (SIC) criteria were created by the International Society on Thrombosis and Hemostasis to categorize sepsis and coagulopathy. SIC values > 4 are associated with greater severity of illness highlighting the importance of prompt recognition and appropriate escalation. The American society of Hematology recommended the monitoring of platelet count, PT, aPTT, D-dimer and fibrinogen emphasizing the role of D-dimer as a marker of severity of infection[7].

Management Strategy of thrombosis in COVID-19 patients

Regarding management of thrombosis in COVID-19 patients a recent study examined two groups of patients having elevated D-dimer with and without COVID-19.1 The COVID-19 group with D-dimer levels (>6 times the upper limit of normal) showed lower mortality rate with heparin administration (Low molecular weight heparin 40-60 mg of enoxaperin per day) or unfractionated heparin (10000-15000 units/day) than those without heparin. Interestingly, there is no difference in

mortality in the COVID-19 negative patients with the use of heparin when stratified by D-dimer level.

Heparin has previously been shown to play an anti-inflammatory role and to offer endothelial protection. Its antiviral effect is also being studied in experimental models and is an avenue that requires further study. Generous use of thromboprophylaxis may help improve outcomes especially in those at high risk of VTE. Kolok et al.[6] studied 184 ICU patients; 23 (13%) patients died and 22(12%) were discharged. The remaining 139 (76%) were still in the ICU ; 31% had thrombotic complications despite receiving low molecular weight heparin (subcutaneous dose of 2850 IU or 5700 IU per day dependent on body weight or date of treatment). From this study it is evident that thrombotic complications are high despite thrombi prophylaxis. Obi[14] et al. observed during H1N1 pandemic that those with ARDS were at increased risk of VTE. They found that those without anticoagulation were 33 times more likely to develop any VTE than those who were treated with empirical systemic intravenous heparin anticoagulation (aiming for a target partial thromboplastin time of 50-70 seconds). Therefore, a similar approach may be necessary for COVID-19 patients to prevent these complications from occurring[7]. However in a study including 407 patients who were considered at high risk of VTE it was found that 44 (11%) patients were at high risk of bleeding. Therefore regular monitoring adjustment of thrombi prophylaxis and correction of coagulopathy are also crucial in preventing complications. Also D-dimer level should be evaluated on daily basis to assess the progress in such patients in terms of VTE risk[7]. Rivaroxaban has been another drug used to combat thromboembolism in COVID patients. For high risk patients at the time of discharge from hospital, Rivaroxaban 10 mg daily for 31 to 39 days, or Betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days have been recommended[15,16]. Rivaroxaban has also been widely used in mild to moderately symptomatic patients with risk factors.

The platelet count may be an affordable and accessible biomarker for assessment of disease severity and risk of coagulopathies. Similarly elevated plasmin has been seen in the setting of acute respiratory distress syndrome and may be useful as a biomarker in COVID-19 patients. The use of point of care ultrasound screening for DVT may also be necessary and others have also been suggested this in the context of COVID-19[7]. The management strategies of combating thromboembolism as adopted by different societies has been portrayed in table 1.

Table 1

Thrombo-prophylaxis recommendation of different authorities

Authority/Last update	Thrombo-prophylaxis recommended	Drug	Adaptation of Dose recommended	Post- discharge prophylaxis
American Society of Hematology (ASH) (Updated: July 20, 2020)	Yes, standard dose in all hospitalized patients. Mechanical only if pharmacological contraindicated. Combination not recommended.	LMWH over UFH	Not by disease severity. May be for obesity. No recommendation for biological parameters.	Not in general. Only if VTE risk is high.
International Society on Thrombosis, Hemostasis, (March 25, 2020)	Yes, standard dose; in all hospitalized patients. Multi-modal with mechanical methods in ICU patients.	LMWH over UFH	Intermediate-dose if high risk ICU patients. Dose modification in obesity. Not recommended by biological parameters.	Yes, LMWH or DOACs for 2-6 weeks if VTE risk is high and bleeding risk is low.
CHEST Guideline and Expert Panel Report by American College of Chest Physicians (updated: June 2, 2020)	Yes, standard dose in all hospitalized patients. Mechanical if pharmacological contraindicated. Combination not recommended.	LMWH or fondaparinux over UFH or DOACs	No. No recommendation for biological Parameters.	Yes, if low risk of bleeding.
National Institutes of Health (NIH), USA (Updated: July 17, 2020)	Hospitalized patients as per standard of care for non-COVID hospitalized patients. No recommendation made on mechanical.	As per standard of care for non-COVID hospitalized adults.	As per standard of care for non-COVID hospitalized adults. No recommendation for biological Parameters.	Not in general. Only if VTE risk is high and bleeding risk is low as per non-COVID-19 patients.
Clinical Management of COVID- 19 by World Health Organization (updated: May 27, 2020)	Yes, in all hospitalized as per local and international standards. Mechanical if pharmacological contraindicated.	LMWH	No mentioned	No mentioned
National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19), Bangladesh (Updated: May 28, 2020)	Yes, in all hospitalized Patients, and also in mild cases with risks. No recommendation made on mechanical.	LMWH or UFH	Yes. Increasing dose of LMWH according to disease severity,D-dimer, oxygen requirements or clinical suspicion or confirmation of VTE.	Extended-use of DOACs for 1 month.

CONCLUSION

COVID-19 patients are in increased risk of thrombosis and embolism due to infection related inflammation, immobility and hypercoagulable state. Adequate thromboprophylaxis with administration of anticoagulation should be administered in all

moderate to severe COVID-19 patients including patients of comorbidity and aged patients. Unfractionated heparin, Low molecular weight heparin, Rivaroxaban and Betrixaban have been used prophylactically and therapeutically to combat thromboembolism. However, many issues are yet to be explored regarding thrombosis and embolism in COVID-19 patients by multicentric multinational large scale studies.

REFERENCES

1. Worldometer website. Available at https://www.worldometers.info/coronavirus/. (Accessed 17th November 2020).
2. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost, 18 (2020), pp. 1094-1099.*
3. Mei H, Hu Y. Characteristics, causes, diagnosis and treatment of coagulation dysfunction in patients with COVID-19. *Zhonghua Xue Ye Xue Za Zhi, 41 (2020), p. E002.*
4. Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet. 2020;395(10224): 565-574.*
5. Jean M, Connors and Jerrold H.Levy. COVID-19 and its implication for thrombus and anticoagulation; *Blood.2020; 135(23):2033-2040*
6. Klok F, Kruip M, Van der Meer N, Arbous M, Gommers D, Kant K, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020 Apr 10. [Epub ahead of print].
7. Hussain I, Savarimuthu S, Tsun leung M, Harky A. The Need to manage the risk of thrombi embolism in COVID-19 patients; *vasc.Surg 2020; 1-6.*
8. Bikdeli B , Madhaban MV, Jimenez D, Chuich T, Dreyfus I, Driggin E et al. COVID-19 and Thrombotic or Thromboembolic Disease : Implications for prevention, Anti thrombotic therapy, and Follow up ; *j Am Coll Cardiol.2020;75:2950-73.*
9. Tang et al. Abnormal coagulation parameters are associated with poor prognostic outcome patients with novel coronavirus pneumonia. J Thomb Haemost 2020 ;18 :844-7.
10. Deshpandeb C et al, Thromboembolic findings in COVID-19 Autopsies : Pulmonary Thrombosis or Embolism? ; Annals.org May 2020 available http://DOI.ORG/10.7326/M20-3255
11. Wichmann et al. Autopsy Findings and Venous Thromboembolism in Patients with COVID- 19: A Prospective Cohort Study. *Ann Intern Med. 2020 May 6 : M20-2003*
12. Lax et al Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series. *Ann Intern Med. 2020 May 14 : M20-2566.*
13. Maraone E Rindaliu. Upsurge of Deep Venous Thrombosis in patients affected by COVID-19: preliminary data and possible explanations. *J Vasc Surg Venous Lymphat Disord 2020 Apr* [Epub ahead of print].
14. Obi A, Tignanelli C, Jacobs B, Arya S, Park P, Wakefield T, et al. Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients. *J Vasc Surg Venous Lymphat Disord* 2019;7:317-24.
15. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE Risk score and elevated D-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open*. 2020;4(1):e59-e65.
16. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med.* 2016;375(6):534-544.