Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

COVID-19 infection and thrombosis

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ABSTRACT

Background: Recent reports on outbreak of SARS-CoV-2 coronavirus (COVID-19) have shown its association with abnormal blood clots. The viral infection initiates inflammatory responses leading to endothelial damage and coagulation cascade dysfnction. Spread of COVID-19 has been associated with disseminated intravascular coagulation (DIC) and subsequent coagulopathy. Initially coagulopathy in COVID-19 patients result in significant elevation of D-dimer, fibrin/fibrinogen degradation products (FDP), and abnormalities in coagulatory parameters, which resulting in formation of thrombus and eventually death.

Methodology: Present report intends to summarize the information of the research reports available so far on the complications of formation of unusal blood clots (thrombosis) during COVID-19 infection and its therapeutic strategies. Extensive web search was done for various reports associating COVID-19 infection with increased coagulopathy and abnormal coagulatory parameters such as PT, PTT, and platelet counts; along with increased D-dimer and fibrinogen levels.

Results and conclusion: Findings of these research reports were summarized to recommend cautions for clinicians while treating COVID-19 patient. Screening of coagulatory parameters upon admission and during entire course of treatment is recommended, especially those who are at increased risk of thrombosis. Also, anticoagulant treatment can be used as thromboprophylaxis measure. Dose and duration of anticoagulation treatment requirement may vary and thus regular monitoring is needed.

Dear editor

An outbreak of Coronavirus disease 2019 (COVID-19) occurred in Wuhan, China in December 2019 and has spread rapidly across the globe. Emergence of the coronavirus disease, represents a pandemic of enormous proportionworldwide. This viral respiratory illness is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in novel coronavirus pneumonia (NCP). It is accompanied with excessive inflammation, hypoxia, immobilization and disseminated intravascular coagulation (DIC). These conditions may predispose a patient to venous and arterial thromboembolism [1–4], thereby further complicating the pathological condition and increasing life threatening risk. Several studies have provided evidence that coagulation dysfunction is a major cause of death in severe COVID-19 patients [1–4]. Awareness regarding thrombotic complications in COVID-19 patients is extremely important for deciding the appropriate course of treatment.

A large number of COVID-19 infected patients have been reported to have other chronic diseases such as cardiovascular disease, malignancy, respiratory diseases and kidney and liver abnormalities. Presence of such comorbidities results in increased severity of COVID-19 infection. Increasing viral load during COVID-19 infection progression leads to cascade of events like inflammation and sepsis releasing inflammatory cytokines which in turn leads to increase in circulating thrombin levels. As a response to severe infection, cytokines play a mediatory role in systemic activation of coagulation and subsequent fibrin deposition [5,6]. The point of impact on coagulation system is tissue factor (TF) VIIa (extrinsic pathway) [7,8], which provides a trigger for cross talk between coagulation and inflammatory pathway [9]. In addition to this, impairment of anti-coagulation pathway as well as fibrin removal by a suppressed fibrinolytic system is also reported [10]. Inflammation induced coagulation activation is characterized by intravascular deposition of fibrin [11]. Inflammatory changes further lead to activation of fibrinolytic system resulting in elevated D-dimer and fibrin degradation product (FDP) levels. Thus there is ample evidence linking inflammatory activation with thrombosis during severe infections [12]. Hyper-inflammatory state also induces endothelial damage. Vascular endothelial cells play a key role in mechanisms that contribute to inflammation induced activation of coagulation. Endothelial cells respond to cytokines released by leukocytes and also release cytokines themselves [13]. They express cell adhesion molecules and growth factors, thereby promoting inflammatory response and coagulation as well [12]. With the disruption of endothelial barrier, coagulation cascade is activated and thus patients exhibit hypercoagulable state which may lead to development of clinical manifestations of venous thromboembolism (VTE) such as a pulmonary emboli (PE) or deep vein thrombosis (DVT). Various recent reports have shown increasing concerns of hypercoagulability in COVID-19 patients [14,15]. Higher incidences of thrombotic complications have been observed in COVID-19 patients admitted in Intensive Care Unit (ICU). Reports have also shown that coagulopathy in COVID-19 infection results in higher D-dimer levels and subsequently high mortality rates [14] and this mortality is reduced by the use of anticoagulation therapy with heparin [15]. Tang et al. studied various coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), antithrombin (AT), fibrinogen, D-dimer and fibrin degradation products (FDP) in 183 NCP patients in Tongji Hospital, Wuhan, China, and found that during the late stages of coronavirus infection, patients have been found to have

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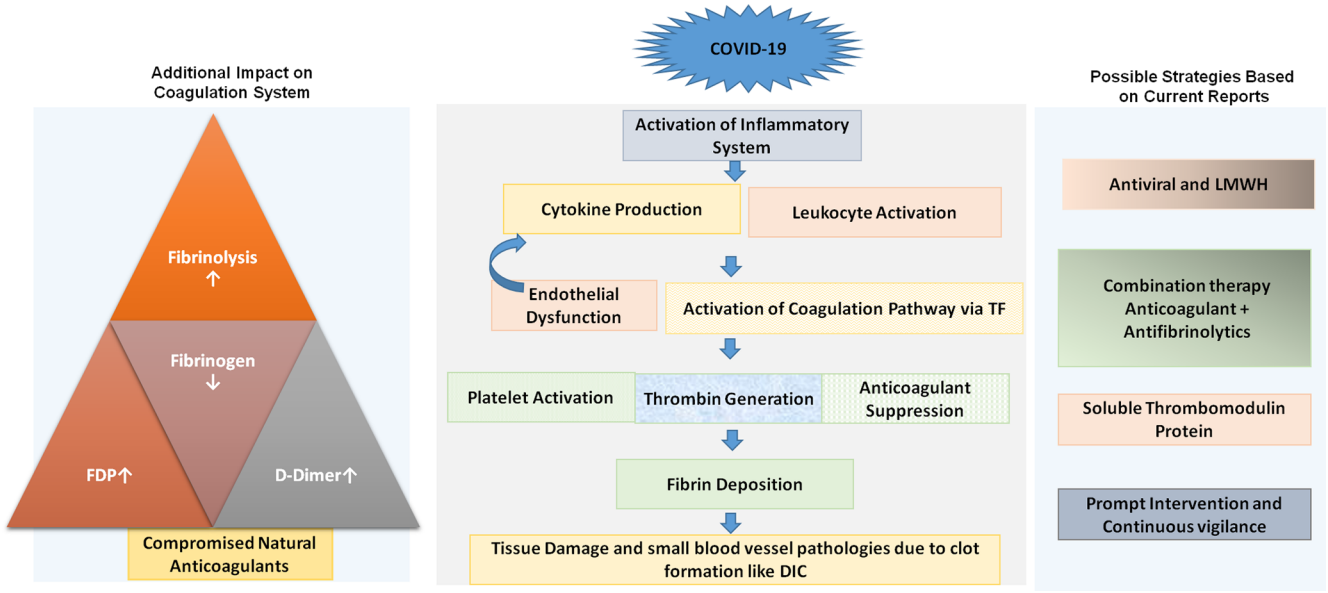

Fig. 1. Possible thrombotic mechanism during Covid-19 infection and suggested treatment strategies.

prolonged prothrombin (PT) and partial thromboplastin time (PTT) along with decrease in fibrinogen and anti-thrombin levels and marked increase in D dimer levels [14]. Also, 71.4% of non survivors and 0.6% of survivors showed evidence of apparent DIC levels during their hospital stay [14]. Thus, abnormal coagulation parameters, especially increased D-dimer and FDP levels are associated with deaths in COVID-19 patients. In another retrospective conducted by the same group, they compared 28-day mortality between heparin users and non-users with different risk of coagulopathy based on sepsis-induced coagulopathy (SIC) score or D-dimer result. This study was conducted on 449 severe COVID-19 patients and 99 of them received low molecular weight heparin (LMWH) treatment for 7 days or longer. Their data revealed that 28-day mortality of heparin users were lower than nonusers. They further reported that among patients had higher mortality rates and raised D-dimer levels in absence of heparin treatment and LMWH treatment was associated with better prognosis in severe COVID-19 patients [15].In yet another study of coagulation parameters in 81 severe NCP patients admitted to ICU, of Union Hospital, Wuhan, incidence of VTE was 25% (20/81), with 8 deaths due to VTE [16]. Researchers further stated that VTE incidence in severe NCP patients was the prime cause of their poor prognosis and significant increase in the D-dimer levels could be a good parameter for identifying high VTE risk amongst COVID-19 patients.

Furthermore, the abnormality in coagulation in COVID-19 differs from what is typically found in other infectious diseases. In the non-survivors of COVID-19 there was a marked decrease in fibrinogen levels and elevation in FDP. This indicated that these patients had disseminated intravascular coagulation (DIC) with enhanced fibrinolysis [14,15] rather than DIC with decreased fibrinolysis, as observed in other infectious disease, wherein fibrinogen levels are not decreased and there is a mild elevation in FDP and D dimer levels [17]. Most recent reports demonstrate that D dimer levels are significantly increased in COVID-19 non-survivors and thus its prognosis can be predicted based on this parameter [1,4,18]. Though Tang et al. recommend use of LMWH for improving prognosis of patients with elevated D dimer levels [15], another drug Nafamostatmesylate (NM) has featured recently for its effectiveness against coronaviruses. NM has been used in Japan from past few decades for treating for pancreatitis and DIC. It is basically a serine protease inhibitor that potently inhibits proteolytic enzymes like thrombin, plasmin, and trypsin [19]. NM possesses potent antifibrinolytic actions [19] and is believed to block requisite viral entry process of coronavirus, thereby limiting spread [20,21]. Asakura et al. suggested combination therapy of heparin and Nafamostat against COVID-19 infection [22]. Other recent reports also suggest thromboprophylaxis for all hospitalized COVID-19 patients [23].

During these unforeseen conditions with worldwide pandemic of coronavirus, it is extremely important to consider risk of thrombotic complications while treating an infected COVID-19 patient. Anticoagulation therapy along with antiviral treatment could be extremely important for patients with a history of thrombosis, or those who are at a higher risk of developing thrombosis [15]. However, dose of anticoagulant and its optimal duration needs to be critically decided by regular monitoring of coagulatory parameters of the patients. Coronavirus infection challenges both innate immunity as well as haemostatic system in patient's body, which if not treated by prophylaxis may lead to severe pathological complications as reported in many patients (Fig. 1). In addition, supportive care is very much required to maintain critical organ function. Levi et al. suggested that in patients with higher concentrations of D-dimer and sudden respiratory insufficiency deterioration, a check for pulmonary embolism should be part of differential diagnosis [24].

COVID-19 patients admitted to the ICUs and receiving mechanical ventilation, along with presence of presence of central venous catheters and being immobile, may together attribute to formation of a thrombus in lungs (PE) or in the lower extremities (DVT). Patients having other pro-thrombotic factors such as obesity, presence of tumor or advanced age may be particularly at a higher risk. In addition to these, a patient could be genetically pre-disposed to thrombotic complications due to various mutations such as those having deficiency of natural anticoagulants or those with elevated coagulation factors. We suggest that, such patients may be given anticoagulant prophylaxis with low molecular weight heparin or unfractionated heparin, provided they are not at increased risk of haemorrhage, along with anti-viral treatment. The current information will be helpful in guiding clinicians for appropriate anticoagulation therapy but vigilance and monitoring is utmost important when implementing on mild and severe COVID-19 infected patients. There is persistence of scanty information regarding use of anticoagulation therapy like proper timing/dosage/administration scheme. So, it is suggested that existing regime should be updated with new information coming from various emerging case reports.

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