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-induced coagulopathy and observed benefits with anticoagulation

Recently, literature recognized an association between coronavirus disease-19 (COVID-19) and coagulopathy [1]. COVID-19 illness severity is positively correlated with coagulopathy markers, including prolonged prothrombin time, increased fibrin degradation products, decreased platelet count, and elevated D-dimer [2–8]. However, the pathogenesis of COVID-19-induced coagulation and the role of anticoagulation treatment remain unclear.

Presence of intravascular and extravascular fibrin is a prominent feature of sepsis-induced acute lung injury [9]. COVID-19 is identified as a sepsis-inducing pathogen, which may contribute to low PaO2 levels associated with decreased arterial blood perfusion secondary to sepsis and coagulopathy [10]. An observational study reported that many critically ill COVID-19 patients presented with clinical manifestations of shock, indicating vascular endothelial dysregulation [10]. Additionally, COVID-19 is characterized by an increase in pro-inflammatory markers, such as IL-6 and IL-Iβ, and induction of cytokine storms. Such events cause alveolar thickening, hyaline membrane formation, diffuse organ damage, and microthrombi via coagulation cascade activation which contributes to low SpO2 [11]. In fact, the pulse oximeter may inaccurately identify blood oxygen saturation (SpO2) in COVID-19 patients due to sepsis-induced vasodilation, formation of arteriovenous shunts, and culmination of venous blood containing carbon dioxide (CO2) [12].

An observational study identified thrombotic event incidence in COVID-19 patients who received nadroparin 2850 IU or 5700 IU (if body weight was > 100 kg) subcutaneous per day as thromboprophylaxis [13]. Venous Thromboembolism (VTE) in 27 % of patients (95 % Confidence Interval (CI) 17–37 %) and arterial thrombotic events in 3.7 % of patients (95 % CI 0–8.2 %) were confirmed with computed tomography pulmonary angiography (CTPA) and/or ultrasonography. Of these events, pulmonary embolism (PE) was the most common complication (n = 25, 81 % of all thrombotic events) [13]. A subsequent Italian observational study reported 16.7 % (95 % CI 8.7–29.6 %) of a total of 48 intensive care unit (ICU) patients had at least one thromboembolic event, although all patients received thromboprophylaxis with weight adjusted low-molecular-weight heparin (LMWH). This study also found that 6.4 % of 314 ward patients (95 %CI 4.2 %–9.6 %) experienced at least one thromboembolic event. For the total patients, pulmonary embolism makes up 35.7 % of all reported complications. This study presented a higher incidence of thromboembolic events in patients admitted to ICU compared to general ward patients. In a recent case series, Negri et al, (2020) explored the effect of dose-titrated heparin on the PaO2/FiO2 level. During the first 72 h of heparin administration, all 27 patients experienced improved oxygen partial pressure (PaO2 in mmHg) to fraction of inspired oxygen (FiO2) ratio compared to pre-coagulation treatment($p = 0.013$) [14]. Specifically, 6 patients received heparin or enoxaparin in prophylactic doses, 3 patients received enoxaparin (0.5 mg/kg twice daily), and 18 patients received enoxaparin (1 mg/kg twice a day) or full dose heparin without death or complication [14]. Unlike the two previous studies, Negri et al, (2020) titrated the LMWH according to D-dimer level and increased the dose in patients presented with deoxygenation or thromboembolic events. No patients experienced bleeding complications despite increasing the dosage of heparin. The improvement of PaO2/FiO2 upon receiving anticoagulation suggests that micro-emboli secondary to coagulopathy may cause V/Q mismatch. This may partially explain the high mortality rate for patients on ventilation, as ventilating a lung with decreased circulation is ineffective [15]. This is supported by post-mortem assessment of pulmonary tissues in COVID-19 patients that revealed microthrombi and diffuse alveolar damage from thrombotic microangiopathy which may be a plausible mechanism of fatality [16,17]. Additionally, if PaO2/FiO2 can be improved, the use of therapeutic anticoagulation should be explored in COVID-19 patients with acute respiratory distress syndrome.

Presenting features of thrombosis in COVID-19 are not limited to microvesseles. Thrombotic events, such as large vessel occlusion (carotid and cerebral arteries), were reported in 5 patients < 50 years of age [18]. A recent retrospective study of 2773 COVID-19 hospitalized patients determined longer periods of anticoagulation treatment were correlated with reduced mortality risk with a multivariate proportional hazards model (adjusted Hazards Ratio (HR) of 0.86 per day; 95 % confidence interval: 0.82 to 0.89; $p < 0.001$) [19]. A second study reported lower 28-day mortality rates among COVID-19 patients with sepsis-induced coagulopathy (SIC) score ≥ 4 (40.0 % vs 64.2 %, P = .029), or D-dimer > 6 times the normal upper limit (32.8 % vs 52.4 %, P = .017) in a heparin-treated group compared to a non-heparin-treated group [2]. Based on the current evidence, the role of anticoagulation in critically ill COVID-19 patients may have a benefit, further studies are needed to investigate the extent of benefit and recommended target dosing for patients.

Currently, there are limited specific guidelines for anticoagulation prophylaxis and treatment in patients with COVID-19. Leading professional organizations, such as the American Society for Hematology, are currently developing evidence-based guidelines as more data are collected and analyzed [20]. Their current resources recommend that despite the abnormal PT, or PTT, that all patients hospitalized with CoVID-19 should receive a prophylactic dose of low molecular weight heparin, and held only if platelet count is less than 25×10^9/L, or fibrinogen level is less than 0.5 g/L. The National Institutes of Health (NIH) recommends that VTE prophylaxis should be given for all hospitalized adults with COVID-19 per standard of care [21]. The CDC (2020) noted a paucity of data and did not provide recommendations, however, did state that elevated D-dimer levels are associated with a greater risk of death [22]. Therefore, for patients without contraindications to anticoagulation therapy, it may be logical to titrate heparin dosing according to D-dimer level. Negri et al, (2020) completed this without any bleeding complications or fatalities within 72 h of administration.

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In conclusion, more studies must be conducted to evaluate the safety and benefit of titrating low molecular weight heparin to D-dimer. Additionally, therapeutic anticoagulation in the context of ARDS should be explored, as preliminary findings show an increase in PaO2/FiO2 following anticoagulation in COVID-19 infected patients.

CRediT authorship contribution statement

Sedighe Karimzadeh: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing - original draft, Supervision. **Vinh Dong:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing - original draft, Supervision. **Osama Gamal Hassan:** Formal analysis, Investigation, Writing - review & editing. **Akshay Raut:** Formal analysis, Investigation, Writing - review & editing. **Ahmed Fouda:** Formal analysis, Investigation, Writing - review & editing. **Allison Parrill:** Formal analysis, Investigation, Writing - review & editing. **Kimberly Eaton:** Formal analysis, Investigation, Writing - review & editing. **Nguyen Tien Huy:** Supervision, Formal analysis, Project administration, Writing - review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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