EDITORIAL

COVID-19 INFECTION AND RISK OF THROMBOEMBOLISM

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COVID-19 has emerged from China and spread throughout globe since December 2019. The causative pathogen is recognized as novel enveloped RNA beta-coronavirus, [1] having similar genetic structure to SARS-CoV, and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has now been declared as public health emergency by World Health Organization (WHO). [2]

Millions of casualties, morbidities and mortalities have been reported worldwide, with number going on. [3-4] The clinical history of the disease is heterogeneous and ranges from mild non-specific symptoms (e.g. dry cough, fever and diarrhoea etc) to lung insufficiency, severe pneumonia and death. In case of lung insufficiency, mechanical ventilation is required or individuals with multiple organ failure, treatment is according to underlying conditions and age. [5] Pro-inflammatory markers are usually associated with the severity of disease including interleukin-2, interleukin-6, interleukin-7, interleukin-10, interferon γ-induced protein-10, granulocyte colony-stimulating factor, macrophage inflammatory protein-1A, monocyte chemotactic protein-1 and tumour necrosis factor-α; though the reason behind this cytokine storm is still not clear. [6] Among various biochemical and clinical parameters which are linked with poor prognosis of the disease, a D-dimer level in high range is good predictor for the development of acute respiratory distress syndrome (ARDS). In Tongji Hospital, Wuhan, China, Tang et al evaluated prognosis of 183 patients with confirmed 2019-nCoV pneumonia. He showed that in patients with COVID-19, disseminated intravascular coagulation (DIC) is frequent cause of disease worsening. Abnormalities of coagulation and increased level of D-dimer were significantly associated with high mortality and co-morbid complications of thromboembolism. The disease was more severe in patients with severe lung failure. [7] Cui et al evaluated 81 patients admitted to ICUs, and described the thromboembolism prevalence rate of about 25%. [8] Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) can reduce the mortality rate in severe patients of COVID-19 if stared at prophylaxis dose, [9] reflecting a score for sepsis-induced coagulopathy (SIC) of ≥4 (40% Vs. 64.2% with p-value of 0.029) or level of D-dimer six times higher as compared to

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normal (32.8% Vs. 52.4% with p-value of 0.017). In affected Italian patients in intensive care unit, frequency of thromboembolic complications is higher (up to 30%). Though, the incidence of deep venous thrombosis in Italian patients without COVID-19 was 0.025%. [10] Median age of included patients was 45.4 years, which may be contributing factors for increased frequency of thromboembolic complications, in contrast to Chinese population with median age of 37.4 years. [4-5] Major thromboembolic complications in Italian patients were pulmonary embolism and venous thromboembolism; all documented by CT scan or compressive ultrasonography.

Almost all patients show variations in parameters of haemostasis including: 1) Increased D-dimer levels (>1,000 at the time of admission, and rapidly rise thereafter); 2) Increased fibrinogen that may be utilized in later stages of disease; 3) Decreased platelet count (thrombocytopenia) but less incidence than disseminated intravascular coagulation; and 4) Normal or sometimes increased partial thromboplastin time (PTT) and international normalized ratio (INR). Other coagulation tests show increased von Willebrand factor levels, increased factor VIII levels, and normal protein C, S and antithrombin III levels. Data from COVID-19 patients in ICU is summarized in Table 1.

Table 1: Coagulation Profile in COVID-19 DIC, Acute DIC and Chronic DIC

Parameters	COVID-19 Disseminated Intravascular Coagulation (DIC)	Acute (decompensated) Disseminated Intravascular Coagulations (DIC)	Chronic (compensated) Disseminated Intravascular Coagulation
Platelet count	Normal/Decreased	Decreased	Variable
Prothrombin time (PT)	Normal/Prolonged	Prolonged	Normal
Partial thromboplastin time (PTT)	Normal/ prolonged	Prolonged	Normal
Thrombin time (TT)	Normal/prolonged	Prolonged	Normal/slightly prolonged
Plasma fibrinogen	Increased	Decreased	Normal/increased
Plasma factor VIII	Increased	Decreased	Normal
Fibrin degradation products (FDPs)	Increased	Increased	Increased
D-dimer	Increased	Increased	Increased

Disseminated intravascular coagulation (DIC) in patients with COVID-19 is a kind that is recognized by hypercoagulability. Yet exact mechanism for DIC in COVID-19 is not clear; though release of cytokine and inflammatory drive may be the contributing factors in impairment of coagulation that lead to thromboembolic complications. Stimulation of interleukin-6 (IL-6) may up-regulate synthesis of fibrinogen by liver and virus may combine directly to endothelial cells and causes damage to alveoli.

Disseminated intravascular coagulation (DIC) seems to be the indicator for severity of disease and associated with poor clinical outcome. [7] From 40 autopsies, ¼ showed macro-thrombosis with classical pulmonary embolism pattern. More than 2/3 demonstrated thrombi in microvessels, related to diffuse damage of alveoli and interstitial lung infiltrates of macrophages, granulocytes and giant platelets. These are in agreement with study by Luo et al. (11) These findings postulate the mechanism of inflammatory-mediated micro- and macro-thrombosis as classical process of damage in COVID-19 severe patients. Improving patient outcome in COVID-19 by different simple and cheap antithrombotic agents is tempting, but to adapt aggressive approach, various factors should be clarified and addressed, especially to define suitable timing to start treatment and dosage that may influence concomitant drug therapies.

Scientific community is working for more strong evidence on role of anti-platelet therapy or heparin in COVID-19-associated coagulopathies, the Italian Society on Thrombosis and Hemostasis published some recommendations, (12) for the management of COVID - 19 - associated coagulopathies (Figure 1-3). 1) Evaluation of individual risk along with laboratory investigations must include function of hemostatis, platelet count and D-dimer; ultrasound screening for deep venous thrombosis (DVT). 2) Treatment with UFH, LMWH or fondaparinux at specified doses indicated for VTE prophylaxis is recommended in all hospitalized COVID-19 patients; patients with contraindications to anticoagulant therapy should be managed with limb compression. Throughout stay at the hospital, thromboprophylaxis should be given, followed by maintenance at home for 1-2 weeks after discharge from hospital. 3) Treatment with intermediate dose LMWH (e.g. enoxaparin 4,000 IU S/C every 12 hours) can be given in patients with multiple risk factors for VTE (e.g. BMI>30, active malignancy or previous VTE etc). In patients with renal failure, activated Xa should be strictly monitored. 4) LMWH or UFH therapeutic doses are not appreciated without evident VTE diagnosis or as bridging strategy in individuals on vitamin K antagonists; though cannot be recommended in all COVID-19 infected patients. 5) Caution should be taken for direct oral anticoagulants and vitamin K antagonists due to interaction with antiviral mediations. 6) Strong cooperation between specialists of various specialities should be made for multi-disciplinary approach in COVID-19 patients.

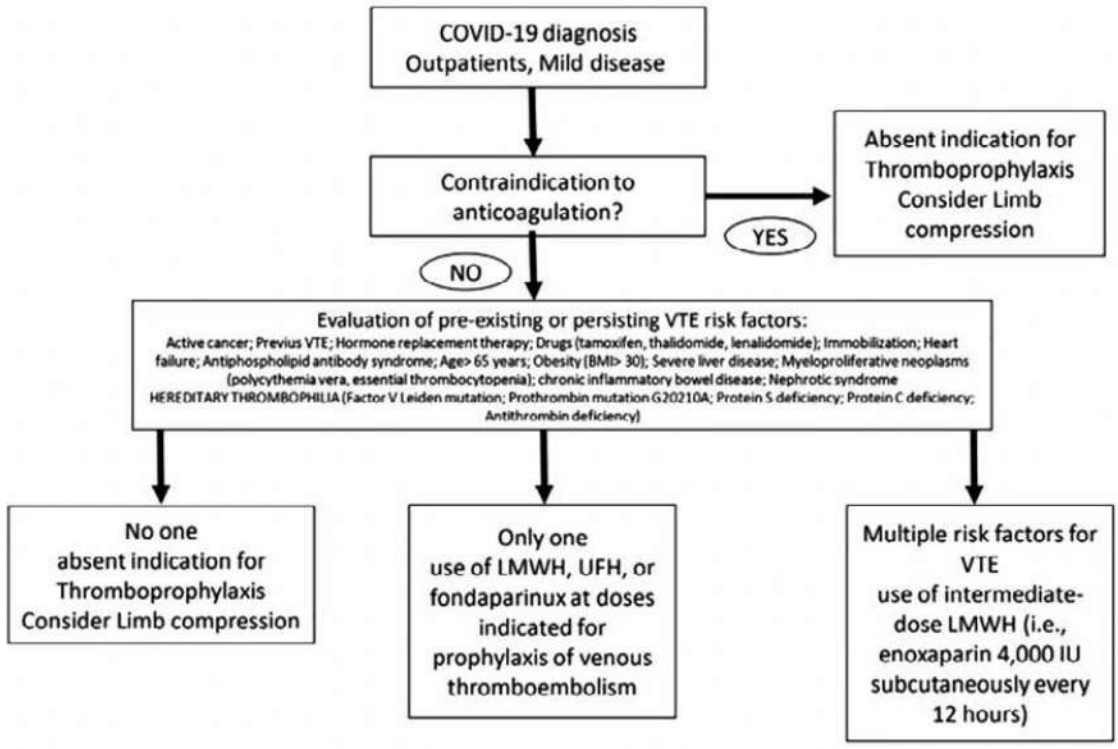

Figure 1: Prophylaxis of Venous Thromboembolism Therapy Scheme for COVID-19 Diagnosed Patients with Mild Disease (adapted from Italian Society of Thrombosis and Hemostasis)

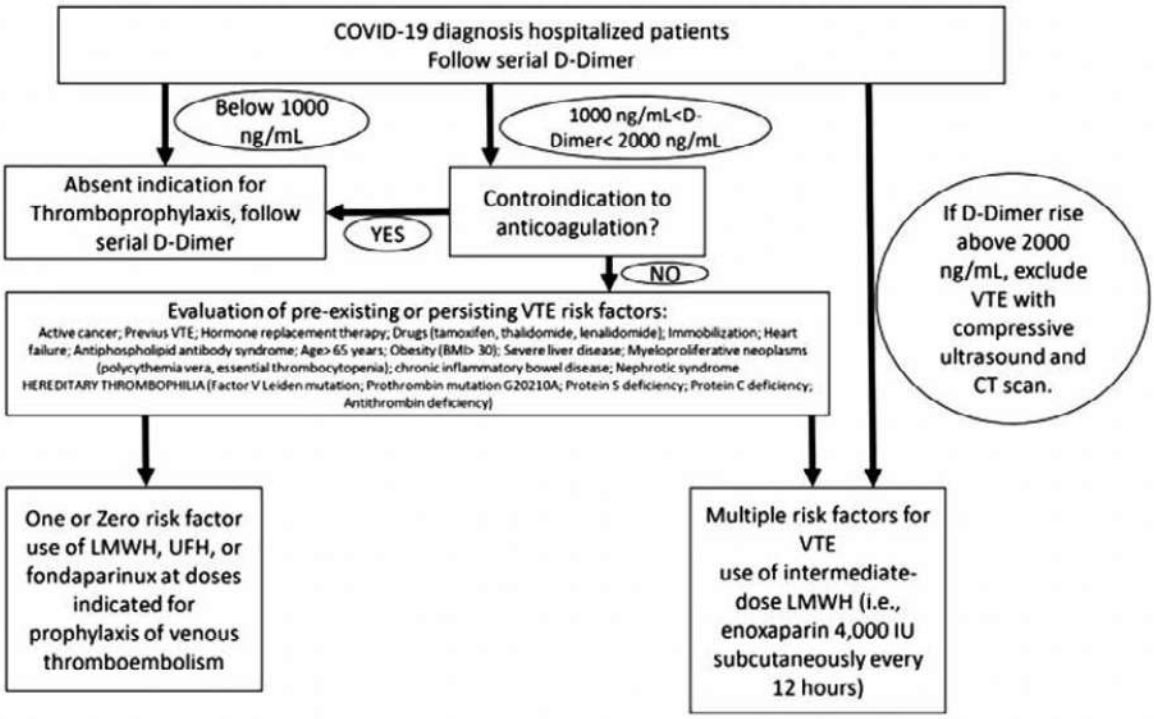

Figure 2: Prophylaxis of Venous Thromboembolism Therapy Scheme for COVID-19 Hospitalized Patients (adapted from Italian Society of Thrombosis and Hemostasis)

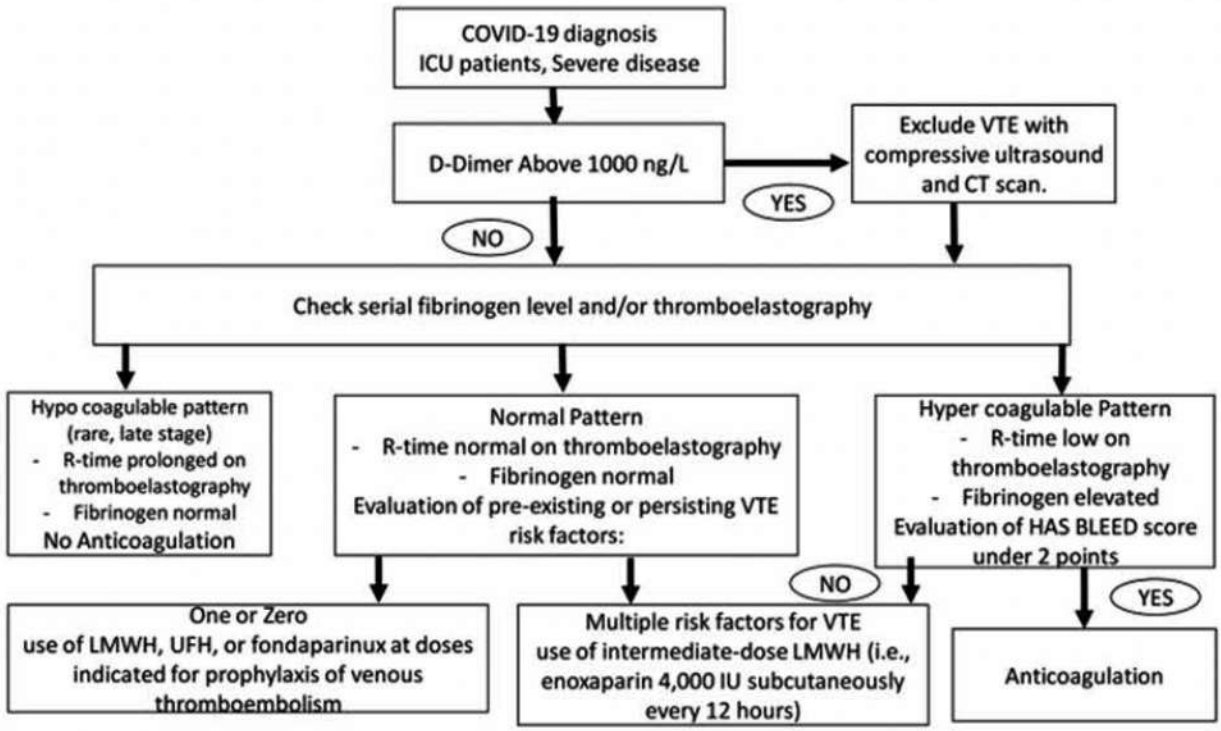

Figure 3: Prophylaxis of Venous Thromboembolism Therapy Scheme for COVID-19 ICU Patients (adapted from Italian Society of Thrombosis and Hemostasis)

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CONFLICT OF INCIDENCE

No conflict of interest declared by the authers.

AUTHORS' CONTRIBUTION

LN - Manuscript Writing