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Covid-19 Infection and Thrombosis

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Abstract

A new coronavirus, called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), emerged in late December 2019, Wuhan (Hubei, China). The disease, now known as COVID-19, has spread rampant and has given rise to a pandemic world that has precipitated draconian measures to limit its transmission. COVID-19 has demonstrated a wide spectrum of clinical manifestations, from asymptomatic or paucisymptomatic forms, to severe viral pneumonia with respiratory failure, multi-organ and systemic dysfunction, and high morbidity and mortality. The body's hyper inflammatory response has been associated, along with the possible direct effects of SARS-CoV-2 on organs throughout the body *via* ACE2. Disseminated intravascular coagulation is another common complication. The inflammatory response caused by COVID-19 in the lung due to the virus itself developing pneumonia, followed by cytokine storm and hemophagocytic syndrome causes a hyper coagulation state manifesting small and large vein and arterial thrombosis and likely DEC. Many hyper coagulation biomarkers such as D-dimer, elevated cytokines such as Il-6, and inflammation parameters such as C reactive protein support this clinical picture. Anticoagulant treatment with heparin and anti platelet should always be ordered.

Introduction

COVID-19 infection produces excessive virus-mediated lung inflammation, cytokine storm, and hemophagocytosis resulting hypoxemia and hypoxia, immobilization of the patient and Diffuse Intravascular Coagulation (DIC), which can predispose to venous and arterial thromboembolism [1-3]. The cardiovascular manifestations observed are deep vein thrombosis, acute Pulmonary Embolism (PE), ischemic stroke, myocardial infarction, or systemic arterial embolism. After an early phase characterized by mild symptoms, patients with COVID-19 infection may develop interstitial pneumonia associated with an acute inflammatory state. The autopsy findings showed occlusion in the small vessels of the lungs and also in other organs, possibly due to an intense secretion of cytokines associated with endothelial deterioration that leads to the activation of the coagulation cascade [4]. A pathological study of the lung specimen showed deposition of microvascular injury complement and thrombosis in the pathogenesis of severe COVID-19 infection [5]. Therefore, knowledge about the incidence of thrombotic complications in patients with COVID-19 is important to determine which and the intensity of thromboprophylaxis. The presence of thrombotic microangiopathy implies a complex mechanism of thrombosis and that prophylactic heparin may be insufficient to prevent the morbidity and mortality of these patients in Intensive Care Units (ICU) [6,7]. Early biomarkers of inflammation and thrombosis are necessary for the control and treatment of severe COVID-19 to prevent the high morbidity and mortality of patients in this clinical phase.

Epidemiology of Thrombotic Manifestations

A Medline study of 660 articles of COVID-19 infection, published from 1/1220 to 2/23/220, 27 were selected for assessment. Finally, 19 of them were included for qualitative and quantitative analyses and 39 case report articles were analyzed separately. The most prevalent manifestations of 656 patients were: Fever 88.7%, cough and dyspnea 45.6% were the most prevalent manifestations and 20.3% of patients required Intensive Care Unit (ICU), 32.8% presented with Acute Respiratory Distress Syndrome (ARDS), 6.2% with shock and 13.9% of hospitalized patients had fatal outcomes [3]. The 20% of polymorbid, COVID-19 infected patients, required ICU. As this virus spreads globally, countries need to urgently prepare human resources, infrastructure and facilities to treat severe COVID-19. But this study seems that the venous and arterial thrombotic manifestations were undervalued in the first recent publications of COVID-19 infection. Venous Thromboembolism (VTE) is more difficult to recognize in intubated patients with a higher threshold for imaging tests

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due to strict isolation of the ICU and thrombosis prevention is with heparin and/or use of mechanical thromboprophylaxis.

Another multi center study of 184 patients with pneumonia proven by COVID-19 [4], admitted to the ICU, with an average observation of 7 days, showed that 23 died (13%), 22 were discharged alive (12%) and 139 (76%) still remained in the ICU. All patients were treated with standard heparin doses for thromboprophylaxis, although the regimens differed between hospitals and the doses increased over time. The cumulative incidence of thrombosis was 31% with 27% of Pulmonary Thromboembolism (PE) and 3.7% of arterial thromboses confirmed by CTPA (Computed Tomography Pulmonary Angiography) and/or ultrasound confirmed. Pulmonary Embolism (PE) was the most frequent thrombotic complication n=25 (81%). The biomarkers and predictors of coagulopathy were spontaneous prolongation of the Prothrombin Time (PT) >3 s or time of Activated Partial Thromboplastin (APTT) >5s. The authors consider that a 31% incidence of thrombotic complications in ICU patients with COVID-19 infection is very high and suggest strictly applying pharmacological prophylaxis of thrombosis in all patients with COVID-19 admitted to the ICU, and increase at high prophylactic doses, even in the absence of random evidence of thrombosis.

A series of 388 patients with COVID-19 infection from Italy [8], hospital of Milan, (mean age 66 years, 68% men) 16% requiring ICU. Thromboprophylaxis was used in 100% of ICU patients and 75% of those in the general ward. Thromboembolic events occurred in 28 patients, the majority in ICU, with an ischemic stroke rate of 3.6% and DIC of 2.2%. More than half of venous or arterial thromboembolism events were diagnosed in the first 24 h of admission, often representing the first manifestation of COVID-19. This suggests the urgent need to improve the diagnosis of VTE and to investigate the efficacy and safety of ambulatory thromboprophylaxis in patients with COVID-19 infection.

According to a Chinese study, the prevalence of VTE was 25% with routine VTE screening, although details on the type and timing of screening were not provided [9]. These values appear much higher than the rate of symptomatic VTE events observed in thromboprophylaxis trials, not exceeding 3% in patients not receiving anti coagulant therapy and <1% on thromboprophylaxis but in line with what observed in patients with sepsis or shock [10-12]. A recent analysis from a French group showed that the rate of thromboembolic complications in 150 COVID-19 patients with ARDS was much higher (11.7%) than what observed in a historical control group of non-COVID-19 ARDS patients (2.1%) despite anti coagulation [13].

Pathophysiology of Thrombosis and Infection COVID-19

Prothombotic biomarker

Acute respiratory failure and a systemic coagulopathy are critical aspects of the morbidity and mortality characterizing infection with severe ARDS associated of COVID-19. The inflammatory response caused by COVID-19 in the lung due to the virus itself developing pneumonia, followed by the cytokine storm and hemophagocytic syndrome causes a state of hypercoagulation that manifests venous and arterial thrombosis of small and large vessels and probable DIC. Many biomarkers of hypercoagulation, elevated cytokines, and parameters of inflammation support this clinical picture.

Procoagulant biomarker

The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia, increased D-dimer levels, which are associated with a higher risk of requiring mechanical ventilation, Intensive Care Unit (ICU) [14] admission, or death, prolongation of PT and International Normalized Ratio (INR), Thrombin Time (TT) shortened APTT.

However, the prolongation or shortening of PT, INR, TT, a PTT depends on the phase of the DIC [15]. Magro et al. [5] report complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection; they examined skin and lung tissues from 5 patients with severe COVID-19 characterized by respiratory failure (n=5) and purpuric skin rash (n=3). No viral cytopathic changes were observed and the Diffuse Alveolar Damage (DAD) with hyaline membranes, inflammation, and type II pneumocyte hyperplasia, hall marks of classic acute respiratory distress syndrome, were not prominent. These pulmonary findings were accompanied by significant deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and Mannose Binding Lectin (MBL)-Associated Serine Protease (MASP) [2], in the microvasculature, consistent with sustained, systemic activation of the alternative and lectin-based complement pathways. The purpuric skin lesions similarly showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin. In conclusion, at least a subset of sustained, severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state. It provides a foundation for further exploration of the pathophysiology importance of complement in COVID-19, and could suggest targets for specific intervention as eculizumab [16].

Recently Zhang et al. [2] describe three patients with Covid-19 infection who presented positive antiphospholipid Protein antibodies (aPl) and coagulopathy. aPl are associated with blood hypercoagulation known as Antiphospholipid Syndrome (APS) [17]. The aPl to the diagnosis of APS are the Anticoagulant Lupus (LA) detected by coagulometric methods and the anticardiolipin (aCl) and antiβ2-glycoprotein-I (anti-β2GP-I) measured by ELISA. aPl are associated with autoimmune diseases, mainly systemic lupus, infectious diseases, without apparent disease or the Primary Antiphospholipid Syndrome (PAPS). A characteristic of the aCl associated with APS is the β2GP-I dependency, since the β2GP-I is an essential cofactor for aCl activity in the ELISA or in the purification of the aCL by affinity chromatography [18,19]. aCl β2GP-I independent antibodies are in infectious diseases and without thrombotic complications. Zhang et al. [2] don't report titers of aCL or anti Beta2GPI IgG or IgA; low levels (<40 GPL), are not usually associated with thrombosis: In our study on aCl IgA in many patients we did not find cases with aCL IgA without aCl IgG [19]. The aCl IgA or IgM have a lot of non-specific binding in the home ELISA and can be falsely positive antibody [20]. In conclusion, more studies on aPl in covid infection [19], are necessary to be able to relate the coagulopathy with aPl antibody.

Procoagulant Activity by Cytokine Storm

The symptom of COVID-19 infected patient's ranges from minimal symptoms to severe respiratory failure with multiple organ failure, including Acute Respiratory Distress Syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure,

coagulation dysfunction, and acute kidney injury. Inflammatory cytokine storm is very common in patients with severe COVID-19. Cytokine Storm (CS) refers to excessive and uncontrolled release of pro-inflammatory cytokines. Una most of severe COVID-19 patients in our ICU ward have persistent very high level of globular Sedimentation Rate (ESR), CRP (C Reactive Protein), and high level of IL-6,TNFα, IL-1β, IL-8, IL2R, etc., and were associated with ARDS, hypercoagulation and Disseminated Intravascular Coagulation (DIC), manifested as thrombosis, thrombocytopenia, gangrene of extremities. It is possible that CS exacerbates lung damage as well as lead to other fetal complications [21]. Notably, there was not pronounce difference of serum IL-6 level been the ICU and non ICU patients. However, in another retrospective, multicentre cohort study, the same study group reported a significantly elevation of IL-6 level in non-survival group of patients with COVID-19, as compared with that of the survivals. Several other reports also confirmed the elevation of IL-6 in critically ill patients with COVID-19 and treatment with anti-Il-6 is being indicated. Angiotensin Converting Enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV [22]. Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2. ACE2 expression was high in lung, heart, ileum, kidney and bladder. In lung, ACE2 was highly expressed on lung epithelial cells. Endothelial cells also express ACE2 he functions of the endothelium includes promotion of vasodilation, fibrinolysis, and anti-aggregation. Because endothelium plays a significant role in thrombotic regulation, hypercoagulable profiles seen in severe diseases likely indicate significant endothelial injury [23]. Endothelial cells also express ACE2 and the endothelial cells represent the one third of lung cells. Microvascular permeability as a result of the endothelial injury can facilitate viral invasion, and they may contribute. Microvascular permeability as a result of the endothelial injury can facilitate viral invasion, and they may contribute thrombotic events.

Procoagulant Activity and Hemophagocytosis by COVID-Infection

Hemophagocytic Lymphohistiocytosis (HLH) is a hyper inflammatory syndrome caused by uncontrolled immune cell activation. Genetic disorders leading to impaired lymphocyte cytotoxicity (Familial Hemophagocytic Lymphohistiocytosis, FHL) or Immune deficiency syndromes are the best characterized risk factor for development of primary HLH. The secondary or reactive HLH or Hemophagocytic Syndrome (HPS) may be by any Infections (i.e. viral, bacterial, parasitic, malignancies or auto-immune and auto-inflammatory diseases [24]. The dramatic presentation of the syndrome includes unremitting fever, visceromegaly, thrombocytopenia, lethargy, seizures, skin rash, pulmonary failure, and cardiac and/or renal involvement, and the mortality rate is 8% to 22%. The most common laboratory findings are due to liver dysfunction, and include low fibrinogen, and high serum triglycerides and ferritin levels. Two highly diagnostic clues are increased plasma concentrations of the alpha chain of inter leukin-2 receptors (also known as CD25) and impaired NK cell activity [25].

The main pathophysiological abnormality in HPS is cytokine dysfunction, which leads to the uncontrolled accumulation and ectopic migration of activated T lymphocytes, antigen-presenting cells and histiocytes, and multi-system inflammation. The pathophysiology of acquired HPS has not been fully defined, but deficient cytolytic activity leads to the persistent activation of lymphocytes and histiocytes, followed by the hypersecretion of pro-inflammatory cytokines and high soluble inter leukin-2 receptor levels that correlate with the prognosis [26]. Many cases have been described of thrombosis, HPS and parvovirus infection [27].

The COVID-19 disease has prominent manifestations from the hematopoietic system and is often associated with a major blood hypercoagulability [28]. Careful evaluation of laboratory indices at base line and during the disease course can assist clinicians in formulating a tailored treatment approach and promptly provide intensive care to those who are in greater need. COVID-19 infection may have the D-dimer that indicates greater severity of the patient. D-dimer levels and prolonged PT are common in patients requiring ICU. Patients with cardiac injury and high troponin levels are associated with high TP, APTT, and D-dimer. Also, an association of ARDS and risk of death was verified with high PT and D-dimer.

The difference in mean D-dimer levels between survivor sand non-survivors was greater than that between ARDS and non-ARDS, suggesting that DIC-related complications may have increased D-dimer levels. Interestingly, levels D-dimer showed a sequential increase in time among non-survivors compared to those who survived. Fibrinogen and AT-III levels were also significantly lower in non-survivors. 71.4% of non-survivors versus 0.6% of survivors met the clinical criteria for DIC during the course of the disease. A prospective study evaluating the coagulation profile of patients with COVID-19, D-dimer, PDF, and fibrinogen levels were markedly higher among patients than healthy controls. Patients with severe disease showed higher values of D-dimer and PDF than those with milder manifestations.

In the above indicate that D-dimer elevation and DIC may be common in patients with severe form of COVID-19 infection.

Procalcitonin, ferritin and C-reactive protein and LDH are biomarker of inflammation and prognosis but not the coagulopathy [28]. No information has been reported on alterations in the proteinogram such as α1 and α2 proteins as biomarker of inflammation.

Hypercoagulation Treatment of COVID-19 Infection

The treatment for covid-19 infection has a viral part and an anti-inflammatory part that can prevent thrombotic coagulopathy. The hypercoagulation of COVID-19 infection begins in the period that goes from moderate symptoms with pneumonia (frequent fever, cough with no obvious hypoxemia and chest CT with lesions) to severe phase with pneumonia, hypoxemia (SpO2<92%) and critical period with ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury. Usually the patient is transferred to the ICU to the best control and usually assisted breathing. This is the phase of most thromboembolic complications with very difficult to the diagnosis and treatment because the patients is usually immobilized, endotracheal intubation and multiple intravenous catheters that make it difficult to perform imaging tests to diagnose thromboembolism or complete anti coagulant therapy. The risk of thrombosis is very high if the patient has a prior history of primary or secondary hypercoagulation. Several investigational agents are being tested in the management of COVID-19, especially for patients who develop severe disease. Some of these drugs have clinically important inter actions with anti platelet or anticoagulant agents. The current treatment of patients with COVID-19 infection is

standardized in antivirals, immunosuppressants-anti-inflammatory drugs and anticoagulation to prevent or treat ICD and thrombotic events. Antiviral treatments should undoubtedly be important in patients with COVID-19. Since CS is common in severe cases and often leads to exacerbation, anti-inflammatory therapy appears beneficial. Glucocorticoids, chloroquine/hydroxychloroquine, immunosuppressants, inflammatory cytokine antagonists (such as monoclonal anti bodies IL-6R, TNF inhibitors, IL-1 antagonists. In this phase, the use of corticosteroids may be justified in concert with the use of cytokine inhibitors. Such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist). Intravenous Immunoglobulin (IVIG) may also play a role in modulating an immune system found in a hyperinflammatory. The dilemma is missing evidence for consensus: Which patient should we treat with an anti-inflammatory regimen and when to start? What is the duration of treatment? Which medication is the best option? The main concern is that anti-inflammatory medications, such as corticosteroids, may delay removing the virus and increasing the risk of secondary infection, especially in those with an immune system impaired. Second, biological agents that target proinflammatory cytokines can only inhibit the specific inflammatory factor, and therefore may not be very effective in slowing CS in COVID-19 where other cytokines may be of significant importance. Third, some anti-inflammatory drugs, such as JAK inhibitors, also block the production of INF-a, which is important in fighting the virus, and may not theoretically be suitable for treating inflammatory CS caused by the virus. Critical patients generally experienced abrupt deterioration within 1 to 2 weeks after initiation, and immediate initiation of anti-inflammatory therapy in this extremely short period of time is likely to achieve a favorable response to treatment.

The prothrombotic mechanism of COVID-19 infection is probablemente multifactorial, it usually happens when the patient is severely in ICU and presents with DIC and multiple arterial and venous thrombotic manifestations. However, possible treatments are limited to anti platelets, heparin-type anticoagulants, anti-vitamin K and new direct-acting anticoagulants. The first is the detection of the hypercoagulation state by biomarkers measuring D-dimers, Prothrombin time, and platelet count (in decreasing order of importance) in all patients who present with COVID-19 infection with o not thrombosis. Primary prophylaxis with heparin phylactic dose, Low Molecular Weigh the Parin (LMWH), is indicated in any patient with COVID-19 infection and more with elevated D-dimer. In the absence of any contraindications (active bleeding and platelet count less than 25/L × 10^9/L; monitoring advised in severe renal impairment; abnormal PT or aAPTT is not a contraindication. LMWH will also protect critically ill patients against venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where pro-inflammatory cytokines are markedly raised [29].

A higher LMWH dose or therapeutic dose may be indicated if thrombotic events occur despite LMWH at prophylactic doses. Anti platelets can be associated with heparin treatment without arterial thrombosis or new thrombotic events despite LMWH at therapeutic doses. Recently an assay with dipyridamole supplementation was associated with significantly decreased concentrations of D-dimers, increased lymphocyte and platelet recovery in the circulation, and markedly improved clinical outcomes of patients with COVID-19 infection in comparison to the control patients [30].

The other therapies for COVID-19 which can only be considered experimental at the moment including anti thrombin supplementation, recombinant thrombomodulin, and hydroxychloroquine based on mitigating the excess thrombin generation hypothesis [30].

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