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Review on the Efects of Corona Virus on Hematological Parameters and Management

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ABSTRACT

COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. The Coronavirus family are enveloped, single-stranded, positive-sense RNA viruses with spike glycoproteins, composed of two subunits S1 and S2 on their surface. The impact of corona virus infection on the hematological parameters are broad. COVID-19 disease has notable hematological manifestations like Lymphopenia, thrombocytopenia, and anemia. Initially thought to affect predominantly the lungs, COVID-19 is a systemic disease with the potential to affect numerous organs systems with the fibrinolytic system widely affected. The American Society of hematology has recommended the use of either low molecular weight heparin (LMWH) or fondaparinux for thromboprophylaxis in COVID-19-associated hypercoagulability, except in cases where the risk of bleeding supersedes thrombosis risk.

Keywords: COVID-19, hematological parameters, hemostasis and virus

INTRODUCTION

At the end of 2019, a cluster of pneumonia cases caused by a novel coronavirus (2019-nCov) were detected in Wuhan, China. Its rapid spread and lack of specific therapeutic strategy resulted in an epidemic [1]. Soon after, this novel virus became a global concern; on January 30, 2020, the World Health Organization (WHO) declared that the epidemic of 2019-nCoV was a public health emergency of international concern (PHEIC), and on February 11, 2020, the WHO designated the disease coronavirus disease 2019 (COVID-19) [2]. COVID-19's high transmission rate and potential to cause a spectrum of systemic diseases makes it imperative for researchers and clinicians worldwide to collaborate and develop a strategy to manage and contain this disease. [3] Some studies have shown a wide range of hematological abnormalities and virus-related coagulopathies in affected patients, resulting in an increased propensity to develop serious thrombotic complications or disseminated intravascular coagulation (DIC) in severe cases [4]. In this review, we looked at the hematological effects of COVID-19 and ways to manage the deleterious effects.

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-strand RNA virus belonging to the family *Coronaviridae* with about 80% genomic similarities with SARS-CoV [5]. The virus is highly contagious, with over millions of confirmed cases causing millions of deaths worldwide [6]. Viral infection is usually known to be associated with abnormal

haematological parameters. Autopsy of patients who died of COVID-19 showed markedly shrunken spleen with reduced lymphocyte, macrophage proliferation, and phagocytosis [7]. Lymphocytes were also depleted in lymph nodes, and all haematopoietic cell lineages were reduced in the bone marrow. The battle against COVID-19 is likely to be a marathon and the pandemic has a major impact on health care systems in many countries [8]. The virus will continue to pose a risk to people without immunity to it.The symptoms of this disease appear with different degrees that start in the first seven days with mild symptoms such as fever, cough, shortness of breath, and fatigue [9]. Afterward, critical symptoms may develop in some patients involving dyspnea and pneumonia that require patient's management in intensive care units to avoid the serious respiratory complications that may lead to death [10]. However, there are no specific symptoms to diagnose coronavirus infection, and accurate testing depends on the detection of the viral genome using the reverse transcription-polymerase chain reaction (RT-PCR) analysis [11]. Unfortunately, COVID-19 is not limited to its country of origin, but it has spread all over the world. Also there is no enough data that characterize the changes in the hematological and immunological parameters in COVID-19 patients.

Coronavirus Pathophysiology

The Coronavirus family are enveloped, single-stranded, positive-sense RNA viruses with spike glycoproteins, composed of two subunits S1 and S2 on their surface [12]. The receptor binding domain (RBD) of the SARS-CoV-2 helps to structurally differentiate it from other coronaviruses [13]. RBD is also utilized to bind ACE-2 receptors found in abundance on respiratory tract cells during the initial infection phase, as well as multiple other organ tissues as the disease progresses [14]. By binding to the ACE-2 receptor on type II pneumocytes of the lung, SARS-CoV-2 can dysregulate the kallikrein/kinin system and initiate the coagulation cascade [15]. The downregulation of ACE-2 leads to angiotensin II mediated vascular dysfunction, also possibly implicated in the development of a hypercoagulable state in infected patients [16]. The thrombotic milieu seen with COVID-19 infection may be a result of direct endothelial and microvascular damage by the virus, followed by inflammation and the excessive release of cytokines which further aids the development of a prothrombotic state [17]. An increase in the complement factor C5b-C9 has been shown to create extensive capillary damage in the lungs and skin of COVID-19 patients [18]. Also an imbalance of the renin-angiotensin aldosterone system (RAAS) creates increased levels of angiotensin II, relative to angiotensin I. This imbalance manifests as

unregulated inflammation and oxidative stress, leading to dysfunctional endothelium, and further contributing to thrombosis [19].There is evidence that ACE-2 receptors are expressed on lymphocytes, which the virus utilizes to cause a direct cytotoxic effect, leading to lymphopenia [20].

Lymphopenia in Corona virus

Lymphopenia has been consistently found to correlate with the severity of COVID-19 infection and might have a predictive value in the clinical setting [21]. In a retrospective cohort including 201 patients, lymphopenia during the disease course was also reported to be associated with the development of acute respiratory distress syndrome (ARDS) [22]. Lymphopenia was frequently encountered in patients requiring ICU care, ranging from 67% to 85% in various case series [23]. Depletion of T cells and NK cells was seen in patients suffering from COVID-19 [24]. Lymphopenia correlated with a high viral load, as reflected by the low cycle threshold value in respiratory samples [25]. SARS-CoV-2 could trigger necrosis or apoptosis of lymphocytes resulting in lymphopenia. The virus induced NKG2A expression and possibly correlated with functional exhaustion of NK and CD8+ T cells at an early stage, resulting in disease progression [26]. A dysregulated/exuberant innate response also contributed to SARS-CoV-mediated pathology [27]. Cytokine storm with elevation of interleukin (IL)-2R, IL-6, IL-1β, IL-8, IL-17, granulocyte colony stimulating factor (G-CSF), tumour necrosis factor-α (TNF-α), IP10, MCP1, and MIP1α was seen in COVID-19 patients and may also lead to lymphopenia [28].

Thrombocytopenia in Corona virus

Thrombocytopenia is a clinical condition recurrently associated with severe SARS-CoV-2 infections [29]. In COVID-19, the extensive damage caused to the bronchoalveolar tissue and the associated endothelial cells by the viral infection often results in intense platelet recruitment to the lungs and consumption due to intense activation, which lead to the depletion of peripheral platelet count [30]. Some patients have also been present with skin manifestations of petechiae or tiny bruises, but there is still no report on massive bleeding [31]. Compared to lymphopenia, thrombocytopenia is less commonly seen in patients suffering from COVID-19. Platelet count has been evaluated as a biomarker to predict the severity of COVID-19 in multiple studies, but the results were confounded by heterogeneity regarding definitions of thrombocytopenia and end points used. Two meta-analyses showed that a lower platelet count is associated with an increased risk of severe disease and mortality in patients with COVID-19 and may serve as a

marker for progression of illness [32]. Dynamic changes of platelets were also reported to be closely related to mortality [33]. An increment in platelets was associated with decrease in mortality, suggesting the role of monitoring platelets in predicting prognosis during hospitalization [33]. A case series including 30 hospitalized COVID-19 patients evaluated the prognostic value of dynamic changes in platelet count and found that a higher platelet to lymphocyte ratio (PLR) at peak platelet count was associated with longer hospital stay and the change in PLR was more prominent in severe patients, which may be caused by cytokine storm provoking inflammation resulting in the stimulation and release of platelet [34]. Experience from previous SARS patients, caused by SARS-CoV-1, suggested that coronavirus could cause thrombocytopenia by direct viral infection of bone mar-row haematopoietic stem cells via CD13 or CD66a, formation of auto-antibodies and immune complexes, disseminated intravascular coagulopathy (DIC), and consumption of platelet in lung epithelium [35]. Several mechanisms by which COVID-19 causes thrombocytopenia have been proposed, including (a) reduction in platelet production due to direct infection of bone marrow cells by the virus, destruction of bone marrow progenitor cells by cytokine storm, and indirect effect of lung injury; (b) increased platelet destruction by autoantibodies and immune complex; and (c) platelet aggregation in the lungs, resulting in microthrombi and platelet consumption [36]. Cytokine storm of severe disease may lead to secondary haemophagocytic lymphohistiocytosis, which can also result in thrombocytopenia [37]. Thrombocytopenia-associated bleeding is uncommon in COVID-19. Other mechanisms have been suggested for thrombocytopenia in COVID-19, including the development of autoantibodies or immune complexes mediating clearance and direct infection of hematopoietic progenitor cells and the megakaryocytic lineage resulting in decreased production of platelets [38].

Anaemia in Corona virus

Anaemia is not a major problem in patients suffering from COVID-19 [39]. In a cohort of 600 patients with COVID-19, only 1.6% of them required blood transfusion, while the transfusion requirement was higher in those admitted to ICU [40]. Various causes of anaemia among patients with COVID-19 have been reported, including blood loss during continuous renal replacement therapy and gastrointestinal bleeding with or without anticoagulant use [20]. Autoimmune haemolytic anaemia was also reported in patients with COVID-19 within a timeframe compatible with the

development of cytokine storm [30]. SARS-CoV-2 can enter epithelial cells of the gastrointestinal tract via the angiotensin-converting enzyme 2 (ACE2) receptor [22]. Haemolytic anaemia is one of the major side effects of ribavirin, but most patients did not require transfusion according to previous SARS experience [33]. Adequate haemoglobin level is important to ensure sufficient tissue oxygenation. Phlebotomy by small volume blood tubes may help to reduce iatrogenic blood loss [11]. Iron replacement should be given to patients with pre-existing iron deficiency anaemia. Use of erythropoiesis stimulating agents in critically ill patients should be cautious if thromboembolic event is a concern [7].

Fibrinolysis in Corona virus

The fibrinolytic system is widely affected in Covid-19. Fibrinolysis is the process of dissolving blood clots, thereby preventing the obstruction of blood vessels [12]. When activated by tissue- or urokinase-type plasminogen activators (tPA or uPA), plasminogen is converted to plasmin, the critical enzyme of this system, whose function is to degrade the deposited fibrin into soluble fibrin degradation products (FDPs). The production of plasmin is physiologically modulated by plasminogen activator inhibitors - 1 and-2 (PAI-1 and PAI-2) [14]. In SARS-CoV2 infection, there is an uncoordinated coexistence of hypercoagulation and hyperfibrinolysis. Although physiological mechanisms provide the generation of antifibrinolytic mediators such as PAI-1, intense fibrinolysis is still a hallmark in about 25% of COVID-19 patients facing venous thromboembolism (VTE) [14]. Newly generated thrombin also promotes the expression of Annexin 2 (tPA receptor) on the endothelial surface, which in turn expands the effectiveness of tPA activation, plasmin production and the systemic increase in D-dimer levels [20].

Management of Corona virus Patients with Haematological Disorders

The COVID-19 pandemic poses a big challenge for the medical community, with a great impact on management of patients with haematological conditions [21]. The American Society of hematology has recommended the use of either low molecular weight heparin (LMWH) or fondaparinux for thromboprophylaxis in COVID-19-associated hypercoagulability, except in cases where the risk of bleeding supersedes thrombosis risk [26]. In those with existing contraindications for anticoagulation, pneumatic compression devices could be initiated instead. Therapeutic anticoagulation is initiated in patients with confirmed cases of VTE, with patient comorbidities and co-existing conditions dictating the choice of treatment either low molecular

weight heparin, unfractionated heparin, or direct anticoagulants [30]. If necessary, reduced antithrombin III levels can be replenished with fresh frozen plasma [33]. In unstable patients or if systemic fibrinolysis is contraindicated, catheter-directed therapies can be utilized [30]. Patients with COVID-19-associated coagulopathy should be evaluated with viscoelastic coagulation tests including thromboelastography (TEG) and a coagulation and platelet function analyzer [23]. In acute coronary syndrome with plaque rupture, the use of dual antiplatelet and anticoagulants is recommended in accordance with standard guidelines, unless contraindicated [25]. Heparin is generally avoided in DIC but is recommended in DIC associated with COVID-19 [8].

CONCLUSION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-strand RNA virus belonging to the family *Coronaviridae* with about 80% genomic similarities with SARS-CoV [5]. The Coronavirus family are enveloped, single-stranded, positive-sense RNA viruses with spike glycoproteins, composed of two subunits S1 and S2 on their surface [12]. The receptor binding domain (RBD) of the SARS-CoV-2 helps to structurally differentiate it from other coronaviruses [13]. RBD is also utilized to bind ACE-2 receptors found in abundance on respiratory tract cells during the initial infection phase, as well as multiple other organ tissues as the disease progresses [14]. The virus is highly contagious, with over millions of confirmed cases causing millions of deaths worldwide [6]. The impact of corona virus infection on the hematological parameters are broad. COVID-19 disease has notable hematological manifestations like Lymphopenia, thrombocytopenia, and anemia. Initially thought to affect predominantly the lungs, COVID-19 is a systemic disease with the potential to affect numerous organs systems. Furthermore, due to the intensive involvement of COVID-19 in the coagulation system, it can be a target to develop future therapies against COVID-19 [25]. Knowledge about COVID-19 is still rapidly evolving and large-scale clinical trials are warranted to assess the effect of SARS-COV 2 on the hematological system and guide the development of treatment options [29]. The American Society of hematology has recommended the use of either low molecular weight heparin (LMWH) or fondaparinux for thromboprophylaxis in COVID-19-associated hypercoagulability, except in cases where the risk of bleeding supersedes thrombosis risk.

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