BLOOD RESEARCH
Volume 55 · Number 2 · June 2020
https://doi.org/10.5045/br.2020.2020121

Perspective

Coronavirus disease-19 and its hematological manifestations

Hye-Ran Kim, Ph.D.[1], Young-Eun Lee, M.S.[2],
Min-Gu Kang, M.D., Ph.D.[3],
Seung-Yeob Lee, M.D., Ph.D.[4],
Jun Hyung Lee, M.D., Ph.D.[4],
Myung-Geun Shin, M.D., Ph.D.[2,4]

[1]College of Korean Medicine, Dongshin University, Naju, [2]Brain Korea 21 Plus Project, Chonnam National University Medical School, Gwangju, [3]Department of Laboratory Medicine, Gwangyang Sarang General Hospital, Gwangyang, [4]Department of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Hwasun, Korea

Received on May 26, 2020; Accepted on May 26, 2020

Introduction

Coronaviruses are enveloped non-segmented positive-sense ribonucleic acid (RNA) viruses that are broadly distributed in humans and other natural hosts. In the late part of 2019, multiple human infection cases of unknown etiology were identified in relation to the Wuhan seafood market (Hubei province, China) and quickly spread worldwide [1]. The responsible organism has been identified as a novel beta-coronavirus (2019-nCoV), now officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical classification of the infection caused by the virus, coronavirus disease 2019 (COVID-19), is summarized in Table 1 [2]. This article describes the mode of infection, characteristic peripheral blood cell count findings, clinical characteristics of COVID-19 infection, characteristic laboratory findings, alterations in blood coagulation, changes in humoral and cellular immune responses, and management of severe COVID-19 patients, as well as hematopoietic stem cell transplantation guidelines for COVID-19 patients and transfusion safety issues.

Angiotensin-converting enzyme-2 (ACE2) as a receptor for SARS-CoV-2

Angiotensin-converting enzyme-2 (ACE2) has multiple physiological roles with trivalent function, such as negative regulator of the renin-angiotensin system and facilitator of amino acid transportation and is widely expressed in various tissues of our body system. ACE2 has been identified as the main host cell receptor of SARS-CoV-2 and plays

Table 1. Clinical classification of COVID-19 patients [2].

Category	Clinical manifestation
Asymptomatic	SARS-CoV-2 nucleic acid test shows positive. Patients have no clinical symptoms or signs and the chest imaging is normal.
Mild	Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea)
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia, and chest imaging shows lesions.
Severe	Pneumonia with hypoxemia (oxygen saturation < 92%)
Critical	Acute respiratory distress syndrome (ARDS). Patients may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction, and acute kidney injury.

a critical role in the entry of the virus. The upper respiratory tract, especially the oral cavity, has a high susceptibility for COVID-19 infection, meaning the need for future infection control strategies in dental clinical practice and daily life [3].

Clinical characteristics of COVID-19

Common clinical and laboratory manifestations are described in Table 2. A similar ratio of male to female patients has been found in COVID-19 cases, with a median age of 57 years. The most common clinical manifestations are fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal problems (39.6%), while the most common comorbidities are hypertension (30.0%) and diabetes mellitus (12.1%). The most common radiological finding is bilateral ground-glass or patchy opacity (89.6%). Allergic diseases, asthma, and chronic obstructive pulmonary disease are not associated with risk factors for COVID-19. Severe cases of COVID-19 are associated with older age, a high number of comorbidities, and more prominent laboratory abnormalities [4].

Characteristic peripheral blood cell count findings

Patients with COVID-19 showed leukopenia, lymphocytopenia, and eosinopenia. Age, platelet (PLT), and PLT-to-lymphocyte ratio (PLR) are the risk factors in severe infections [5]. Platelet number and its dynamic change during treatment are associated with the severity and prognosis of COVID-19. The increased number of platelet and longer hospitalization period are related to cytokine storm. PLR in COVID-19 indicates the severity of cytokine storm, which may act as a new marker for treatment monitoring [5]. Three possible mechanisms of thrombocytopenia in COVID-19 have been proposed [6]. First, SARS-CoV-2 may suppress thrombopoiesis. Coronaviruses can infect hematopoietic cells in the bone marrow, resulting in decreased hematopoietic potential. Human coronavirus (serogroup 229E) enters hematopoietic cells and platelets through aminopeptidase N (CD13) receptors and induces growth inhibition and apoptosis of hematopoietic cells, resulting in abnormal hematopoiesis and thrombocytopenia. Second, SARS-CoV-2 infection may destroy platelets. COVID-19 may result in elevated levels of autoantibodies and immune complexes, leading to the specific destruction of platelets. Third, SARS-CoV-2 infection may trigger increased consumption of platelet. COVID-19 and inflammation result in lung damage. Damaged pulmonary tissues and endothelial cells may activate platelets, resulting in platelet aggregation and microthrombi formation, increasing the consumption of platelets.

Table 2. Common clinical and laboratory manifestations under COVID-19 [5].

Clinical characteristics	Specific manifestations
Common symptoms	Fever (92%), dry cough (75%), fatigue (75%), gastrointestinal symptoms (40%)
Common comorbidities	Hypertension (30%), diabetes mellitus (12%)
Common radiologic findings	Bilateral ground-glass and patchy opacity (90%)
Common abnormal blood findings	Lymphopenia (75%), thrombocytopenia (73%), eosinopenia (53%), D-dimer (43%), C-reactive protein (92%), procalcitonin (35%)

Characteristic laboratory findings

The blood levels of C-reactive protein, fibrinogen, d-dimer, thrombin time, interleukin-6 (IL-6), and glucose disclose the discriminatory power between mild and severe groups of patients with COVID-19. The combined blood level of IL-6 and d-dimer serve as good predictors of severe COVID-19 by the receiver operator characteristic (ROC) curve analysis. IL-6 and d-dimer are closely related with the occurrence of severe COVID-19, and their combined detection shows high specificity and sensitivity for the easy prediction of COVID-19 severity, which has important clinical value [7].

Alteration in blood coagulation and management of severe COVID-19

The prothrombin time and d-dimer levels were shown to be significantly higher in severe COVID-19 patients [0.68, 95% confidence interval (CI), 0.43 to 0.93; I^2=53.7%; 0.53, 95% CI, 0.22 to 0.84; I^2=78.9%, respectively] [8]. However, there were no significant differences in platelet and activated partial thrombin time values between severe and mild patients (-0.08, 95% CI, -0.34 to 0.18; I^2=60.5%; -0.03, 95% CI, -0.40 to 0.34; I^2=79.5%, respectively). Increased d-dimer and prothrombin time values support that disseminated intravascular coagulation may be common in COVID-19. Furthermore, the increase of d-dimer indicates secondary fibrinolysis of the patient. Fibrin clot formation was reported to favor the fight against influenza virus infections, whereas plasminogen led to deleterious inflammation in patients with pulmonary infections. Therefore, fibrinolysis may induce severe COVID-19 in patients. Hospitalized COVID-19 patients, particularly those who suffer from severe respiratory or systemic symptoms, fall within the scope of the acute-illness population at increased risk of venous thromboembolism. Thrombotic complication has emerged as an important issue in COVID-19 patients. More biomarkers in severe cases of COVID-19 should be identified in future research. In addition, there is an urgent need to study the underlying mechanism of coagulation dysfunction in COVID-19. Clinicians have been suggested to monitor changes in coagulation function in COVID-19 patients everyday [8].

Management of COVID-19 coagulopathy

Marked increase in the level of blood d-dimer is associated with high mortality of patients with COVID-19. Multiple organ failure is more likely to occur in patients with sepsis who have coagulopathy, and by blocking the production of thrombin, mortality can be reduced. The available treatment is prophylactic administration of low molecular weight heparin (LMWH). LMWH therapy seems to be associated with a better prognosis in terms of mortality (40.0% vs. 64.2%, P=0.029) [9].

Similar benefits are seen when d-dimer levels are 6 times above the upper normal limit (32.8% vs. 52.4%, P=0.017) [9]. LMWH therapy may protect severe COVID-19 patients from venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory effects. This could be an additional benefit for COVID-19, where pro-inflammatory cytokines are significantly elevated. Bleeding is reported to be rare in COVID-19 cases. There are several different therapies for COVID-19, although at this time, they can be considered experimental. These include antithrombin supplements, recombinant thrombomodulin, hydroxychloroquine based on the relief of excessive thrombin production hypothesis, and immunosuppressive agents, including inhalation therapy. It may be associated with the bidirectional interactions between inflammation and thrombosis.

Changes in humoral and cellular immune responses under COVID-19

There is currently no data on the specific role of humoral, cellular, or innate immunity in patients who have recovered from COVID-19. The proposed relationships between COVID-19 and immune responses are as follows: a) There is an unstable equilibrium between SARS-CoV-2 and the immune system. Viruses induce an immune response that removes infected cells to eliminate the infection while suppressing the immune response. Therefore, the outcome of an infection depends on the immune response that leads to the elimination of the virus and the kinetics of viral replication that leads to immunosuppression. b) There may be an impact of the initial viral load on the course of the infection caused by SARS-CoV-2. A low viral load promotes an efficient immune response and a painless infection, which leads to the immunity of the infected person. Infection with high viral load tends to cause multi-focal respiratory infections, leading to immunosuppression, severe illness, and even death. c) Other modes of SARS-CoV-2 transmission may have roles. Indolent carriers tend to transfer low viral loads to contacts, causing indolent diseases and antiviral immune responses in immunocompetent individuals. This transmission mode may be considered desirable as it leads to herd immunity when achieved in the majority of the population. However, symptomatic carriers can transfer large amounts of viral particles that can cause severe illness. [10].

Hematopoietic stem cell transplantation under COVID-19

As COVID-19 spreads worldwide, the implementation of guidelines for blood and marrow transplantation is needed due to the risk of infection and the possibility of side effects. A panel of experts from the European Society for Blood and Marrow Transplantation recommended guidelines for the transplant units, recipients, and donors of hematopoietic cells (Table 3) [11]. These guidelines will be updated when

Table 3. Recommendations for hematopoietic cell transplantation in COVID-19 based on EBMT [11].

Recipients		
Scenario	Low-risk disease	High-risk disease
Confirmed diagnosis	Deferred for 3 months	Deferred until asymptomatic and 3 negative PCR tests at least a week apart
Symptoms of URTI	Testing with multiplex respiratory viral PCR, consider deferral	Testing with multiplex respiratory viral PCR, consider deferral
Close contact with COVID-19 patient	PCR test for COVID-19, deferred for 14–21 days	PCR test for COVID-19, deferral based on clinical judgment
Travel to high-risk areas or close contact with a person traveling from high-risk areas	Deferred for 14–21 days	Deferral based on clinical judgment
Donors		
Confirmed diagnosis	Excluded from donation	Unclear when can be cleared for future donation
Close contact with COVID-19 patient	Exclude from donation for at least 28 days, monitor closely for symptoms	Follow local guidelines for isolation and testing for COVID-19
Travel to high-risk areas or close contact with person travelling from high-risk areas	Exclude from donation for at least 28 days, monitor closely for symptoms	Follow local guidelines for isolation and testing for COVID-19

Abbreviations: EBMT, European Society for Blood and Marrow Transplantation; PCR, polymerase chain reaction; URTI, upper respiratory tract infection.

new information about COVID-19 epidemiology and clinical outcomes is obtained (www.ebmt.org/ebmt/news/coronavirus-disease-covid-19-updated-ebmtrecommendations-8th-marc h-2020). Following the local guidelines for the separation and testing of possible COVID-19 cases is recommended. In addition, the blood and marrow transplantation strategy should be developed by constructing guidelines according to regional and national circumstances.

Transfusion safety issues under COVID-19

Coronaviruses usually infect the upper or lower respiratory tract, but the shedding of the virus in plasma or serum is common [12]. Therefore, it is possible that coronaviruses can be transmitted by certain blood products. In endemic areas, the increasing discovery of subclinical infections in COVID-19 cases raises concerns about blood safety and coronaviruses. Chang *et al.* [12] have described the current evidence and understanding of the transmission of SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 through blood products, and detailed the coronavirus inactivation methods. Currently, most guidelines have been prepared based on SARS-CoV or MERS-CoV. However, there are many unknowns about how SARS-CoV-2 shares the dynamics and properties of these viruses. Therefore, it is necessary to monitor the current situation and improve the guidelines for transfusion safety.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Xie M, Chen Q. Insight into 2019 novel coronavirus - an updated interim review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis 2020;94:119-24.
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215:108427.
3. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020;126:1456-74.
4. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.
5. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020. [Epub ahead of print]
6. Qu R, Ling Y, Zhang YH, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020. [Epub ahead of print]
7. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 2020;99:1205-8.
8. Xiong M, Liang X, Wei Y. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br J Haematol 2020. [Epub ahead of print]
9. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023-6.
10. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: epidemiological, clinical and immunological features and hypotheses. Cell Stress 2020;4:66-75.
11. Dholaria B, Savani BN. How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? Br J Haematol 2020;189:239-40.
12. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. Transfus Med Rev 2020. [Epub ahead of print]