Hematological changes in patients with COVID-19 (Review)

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Abstract. In December 2019, an emergence of pneumonia was detected in patients infected with a novel coronavirus (CoV) in Wuhan (Hubei, China). The International Committee on Taxonomy of Viruses named the virus severe acute respiratory syndrome-CoV-2 and the disease CoV disease-19 (COVID-19). Patients with COVID-19 present with symptoms associated with respiratory system dysfunction and hematological changes, including lymphopenia, thrombocytopenia and coagulation disorders. However, to the best of our knowledge, the pathogenesis of COVID-19 remains unclear. Therefore, understanding the mechanisms underlying the hematological changes that manifest during COVID-19 may aid in the development of treatments and may improve patient prognosis.

Contents

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1. Introduction

In December 2019, symptoms associated with pneumonia in patients infected with a novel coronavirus (CoV) emerged in Wuhan (Hubei, China) (1). The virus was classified as a new member of the human CoV (HCoV) family and named severe acute respiratory syndrome (SARS)-CoV-2. The disease caused by SARS-CoV-2 was termed CoV disease-19 (COVID-19) (2,3). SARS-CoV-2 is a highly contagious viral particle that has spread across the Chinese and global populations within a few months (4). The seven types of CoV are listed in Table I and include two α-CoVs (HCoV-NL63 and HCoV-229E) and four β-CoVs [HCoV-OC43, HCoVHKU1, SARS-CoV and Middle East respiratory syndrome (MERS)-CoV] (5). SARS-CoV-2 is the seventh member of the family of enveloped RNA CoVs. A recent analysis (6) indicated that SARS-CoV-2 is divergent from SARS-CoV and MERS-CoV, but shares >85% homology with SARS-CoV. SARS-CoV-2 enters cells by interacting with the specific receptor angiotensin-converting enzyme 2 (ACE2; Table I) (7-9), causing clinical symptoms. A retrospective study revealed that COVID-19 may result in multiple clinical symptoms (10). The most common symptoms were determined to be fever (82-98%), cough (48-92%), and fatigue/muscle pain (11-75%), whereas diarrhea (3.7%) and vomiting (5.0%) were less common. Patients with severe infection can exhibit dyspnea and/or hypoxemia, septic shock, acute respiratory distress syndrome, difficult-to-correct metabolic acidosis and coagulation disorders that develop rapidly (11-14). Severe cases have been associated with significant changes in hematological indexes, such as platelet counts, neutrophil/lymphocyte ratio and platelet-to-lymphocyte ratio; these changes may have prognostic value in determining disease severity (15-17). The current treatment strategies for COVID-19 include providing oxygen, mechanical ventilation, intravenous antibiotics and antiviral drugs (11-14,18). However, some severe and critical patients do not respond well to these therapeutic regimens, and there are currently no vaccines against SARS-CoV-2 or specific therapeutic drugs for COVID-19 (11-14). Therefore, timely monitoring of hematological indexes, and further understanding of the mechanisms involved in the development of hematological changes in patients could be helpful in determining prognosis and initiating therapy to improve disease outcomes.

2. Hematological changes in patients with COVID-19

Changes in routine blood tests in patients with COVID-19. Previous studies have reported that patients with SARS and MERS-CoV-infected patients may exhibit some changes in routine blood work, such as lymphopenia, thrombocytopenia and leukopenia (19,20). Similarly, the majority of patients with COVID-19 have been reported to exhibit lymphopenia, and some patients present with thrombocytopenia and leukopenia. Chen *et al* (12) (n=99) demonstrated that 35, 9 and 24% of patients with COVID-19 had lymphopenia, leukopenia and high leukocyte counts, respectively. In addition, patients with COVID-19 (38%) exhibited higher than normal neutrophil counts. Thrombocytopenia and high platelet counts were also observed in 12 and 4% of patients, respectively, and in 51% of patients, reduced hemoglobin was detected. Furthermore, a retrospective study (n=1,099) detected lymphopenia, thrombocytopenia and leukopenia in 82.1, 36.2 and 33.7% of patients with COVID-19, respectively (14). Different studies have also reported varying rates of lymphopenia and lymphopenia/thrombocytopenia in COVID-19 (13,21-24). Compared with symptoms in non-severe patients, severe patients have been reported to exhibit obvious abnormalities. Wang *et al* (11) detected progressive lymphopenia in patients with severe COVID-19 (Table II). The platelet-to-lymphocyte ratio is an inflammatory marker that reflects the extent of systemic inflammation and cytokine storms (15,16). Thus, in severe novel CoV pneumonia cases, dynamic changes in platelet counts and platelet-to-lymphocyte ratios may have significant value in determining disease severity (15-17). In addition to the aforementioned indicators, hypoalbuminemia, C-reactive protein (CRP) and elevated lactate dehydrogenase may be predictors of disease severity. Moreover, in a previous study, the level of angiotensin II in plasma samples from patients with COVID-19 was significantly increased, and was linearly related to viral load and lung injury (21).

Abnormal immune responses in patients with COVID-19. Immune homeostasis is important for eliminating foreign microorganisms and preventing disease in individuals. This balance gets disturbed in patients infected with SARS-CoV-2, and manifests as T-cell depletion and cytokine storms (25). Liu *et al* (21) (n=12) reported a decrease in the number of $CD8^+$ and $CD4^+$ T cells in 77.8 and 22.2% of patients with COVID-19, respectively. In addition, the levels of IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, IFN-γ-induced protein 10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, platelet-derived growth factor, TNF-α and VEGF were found to be higher in the plasma of infected patients in the intensive care unit (ICU) as compared with those in non-ICU patients (13). The levels of IL-2R and IL-6 have also been reported to be significantly higher in severe cases as compared with those in non-severe patients (25,26) Thus, the depletion of $CD4^+$ and $CD8^+$ T cells coupled with cytokine storm may be closely related to the progression of COVID-19 (13,26).

Abnormal coagulation in patients with COVID-19. Patients with COVID-19 have been demonstrated to have high coagulation indexes (Table II). In a study comprising individuals with familial aggregation infection (n=6), two patients (33.3%) had prolonged activated partial thromboplastin time (APTT), two patients (33.3%) had high levels of plasma D-dimer, and three patients (50%) had increased fibrinogen content (27).

It has also been demonstrated that 46.4% of severe patients had high levels of D-dimer ($P<0.001$) (14), and increased D-dimers and decreased lymphocytes were found to be associated with disease progression (11). Previous studies have shown that almost all severe patients with COVID-19 have coagulation dysfunction, such as prolongation of prothrombin time (PT) and APTT, an increase in fibrin degradation products and severe thrombocytopenia (28,29). In addition, multiple organ dysfunction caused by disseminated intravascular coagulation has been reported to be an important cause of death in critical patients with COVID-19 (28,29). Therefore, timely monitoring of dynamic blood coagulation functions may aid in the improvement of treatment and prognosis for patients with COVID-19.

3. Possible mechanisms of lymphopenia and thrombocytopenia in patients with COVID-19

SARS-CoV-2 attacks hematopoietic cells. It has been shown that plasma from patients with SARS-CoV can inhibit the proliferation and differentiation of colony-forming-unit megakaryocytes (CFU-MK). SARS-CoV has also been reported to infect a small proportion of human MK progenitor cells and $CD34^+$ hematopoietic stem cells (30). However, the mechanisms involved remain to be explored.

The S proteins of SARS-CoV-2 and SARS-CoV use a homologous sequence to directly bind ACE2 expressed on $CD34^+$ hematopoietic stem cells, lymphocytes, monocytes and macrophages (31), in order to initiate infection (17,32). SARS-CoV-2 shares 85% sequence homology with SARS-CoV. Furthermore, SARS-CoV has similar antigenic characteristics to those of HCoV-229E (31). HCoV-229E uses CD13 to infect monocytes and macrophages, and induce cell apoptosis (33). CD13 is also present on the surface of human bone marrow (BM) $CD34^+$ cells, MKs and platelets (34,35). Therefore, CD13 may be a candidate receptor exploited by SARS-CoV to enter blood cells (33,36,37). CoVs can also bind to the CD66a receptor that is expressed on the surface of $CD34^+$ cells, myeloid cells, HL-60 cells, MKs, platelets, T lymphocytes and B lymphocytes (38). Therefore, SARS-CoV-2 may invade hematopoietic stem/progenitor cells, lymphocytes and MKs via ACE2, CD13 or CD66a receptors, thereby resulting in cellular apoptosis, inhibited cell proliferation, lymphopenia and thrombocytopenia.

SARS-CoV-2 has been reported to attack cellular hemoglobin, suggesting the abnormal exchange of oxygen and carbon dioxide in patients (39). The structural proteins of SARS-CoV-2 adhere to heme and form methemoglobin before replacing the resident oxygen and iron, and transforming heme into porphyrin (39). Dissociative iron might induce inflammatory reactions mediated by alveolar macrophages. These and corresponding changes can be detected using computed tomography. Subsequently, SARS-CoV-2 dissociates from oxyhemoglobin, carboxyhemoglobin and glycosylated

Table I. A list of known human CoVs and their receptors (7-9).

CoV type	Genus	Receptors
HCoV-229E	α-coronavirus	hAPN (CD13)
HCoV-OC43	β-coronavirus	HLA class I
HCoV-NL63	α-coronavirus	ACE2
HCoV-HKU1	β-coronavirus	Unknown
SARS-CoV	β-coronavirus	ACE2
MERS-CoV	β-coronavirus	DPP4 (CD26)
SARS-CoV-2	β-coronavirus	ACE2

CoV, coronavirus; HCoV, human CoV; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; hAPN, human aminopeptidase N; ACE2, angiotensin-converting enzyme 2; HLA, human leukocyte antigen; DPP4, dipeptidyl-peptidase 4.

hemoglobin, thereby causing dysfunction in the exchange of oxygen and carbon dioxide in heme. Therefore, SARS-CoV-2 behaves analogous to carbon monoxide in initiating cellular hypoxia and pulmonary embolism (39).

Antibodies and/or immune complexes attack hematopoietic cells. SARS-CoV-2 infection can induce immune responses that result in the production of specific antibodies or immune complexes in patients. Thrombocytopenic patients infected with HIV-1 possess antibodies against platelet proteins that cross-react with HIV-1 glycoprotein 160/120 and elevate the levels of circulating immune complexes (40,41). Subsequently, platelets coated with these antibodies or immune complexes are recognized and destroyed by the reticuloendothelial system. Thus, hematopoietic cells expressing similar antigens can also be injured by the immune complexes. Therefore, antibodies or immune complexes mediate cellular damage and can indirectly induce apoptosis or inhibit the proliferation of hematopoietic stem/progenitor cells, thereby resulting in hemocytopenia (42).

SARS-CoV-2 destroys the hematopoietic microenvironment. The microenvironment in the BM serves an important role in regulating hematopoiesis. BM stromal cells, endothelial cells (ECs), osteoblasts, macrophages, extracellular matrix and secreted cytokines form a honeycomb-like hematopoietic microenvironment (43,44). The destruction and dysfunction of ECs and BM mesenchymal stem cells (MSCs) may alter the hematopoietic microenvironment (43,45-47). The ACE2 receptor is also expressed on the surface of ECs and fibroblasts, and is exploited by SARS-CoV in inducing cellular apoptosis (48,49). As such, EC damage due to the virus binding the ACE2 receptor is possible. Therefore, it may be speculated that SARS-CoV-2 affects the BM microenvironment, including ECs, attenuating hematopoiesis and leading to hemocytopenia.

Drug-induced hematopoietic suppression. Antiviral treatment for COVID-19 includes the use of ribavirin and fluoroquinolones (50). One of the main side effects of these drugs is hematopoietic suppression. Moreover, a previous study has demonstrated that Glucocorticoids as an anti-inflammatory drug can change the circulatory behavior of lymphocytes, particularly T lymphocytes, thus causing apoptosis of lymphocytes. Therefore, Glucocorticoid-induced lymphopenia may help explain the decreased lymphocyte content in patients with COVID-19 (51).

Thrombocytopenia caused by lung damage. The BM is the primary site of platelet production followed by the lungs (52). MKs in BM cavities migrate and circulate in the blood to the lungs. During pulmonary circulation, platelets are released from MKs in the pulmonary extraneous blood vessels; this accounts for ~50% of the total platelet population (52). Moreover, blood vessels outside the lung tissue contain mature and immature MKs and hematopoietic progenitors. During thrombocytopenia, there is a reduction in BM-resident stem cells, and these progenitors migrate into the lung and differentiate into different blood cells (52).

Lung injury caused by SARS-CoV-2 can be attributed to the abundant expression of ACE2 on the surface of human alveolar epithelial cells (49). The lungs of patients with COVID-19 exhibit diffuse alveolar damage with pulmonary congestion, edema, formation of a hyaline membrane and fibrosis (53). Extensive alveolar damage reduces the effective capillary bed of the lung, and affects the fragmentation and formation of MKs in pulmonary microcirculation, thereby resulting in thrombocytopenia (54,55). Moreover, virus- or inflammation-induced damage to the hematopoietic progenitors external to the pulmonary vessels may also affect the capacity for migration and differentiation of hematopoietic progenitors in the lung and result in thrombocytopenia (19). Therefore, increased platelet consumption and/or decreased platelet production could directly or indirectly lead to thrombocytopenia.

4. Possible mechanisms involved in coagulation disorders in patients with COVID-19

Patients with COVID-19 exhibit varying degrees of coagulation disorders; severity or COVID-19-associated death have been reported to be associated with significant coagulation disorders (26,28,29). Hemostasis involves the regulation of blood vessels and vascular ECs; this requires coordination between normal platelet function, coagulation, anticoagulation and fibrinolysis (56). An imbalance in any of these processes may result in coagulation dysfunction; however, to the best of our knowledge, the mechanism involved in the development of coagulation disorders in patients with COVID-19 remains to be understood.

Cytokine release syndrome (CRS). Interactions between viruses and the host result in activation of the innate and adaptive immune responses in the body. Inactivation or hyperactivation results in a cytokine storm.

In response to SARS-CoV-2 infection, $CD4^+$ T cells have been reported to be rapidly activated to produce GM-CSF and other inflammatory cytokines. In addition, it has been shown that the SARS-CoV-2 infection of monocytes, macrophages and dendritic cells may result in their activation, and in the secretion of IL-6, TNF-α, and MCP-1. These cytokines and chemokines recruit lymphoid cells and myeloid cells, such as

Table II. Hematological profiles of patients with coronavirus disease-19.

Authors, year (patient cohort)	Lymphopenia, % of patients	Thrombocytopenia, % of patients	Leukopenia, % of patients	High D-dimer, % of patients	(Refs.)
Guan and Zhong (n=1,099)	82.1	36.2	33.7	46.4	(14)
Chen *et al* (n=99)	35.0	12.0	9.0	36	(12)
Liu *et al* (n=137)	72.3	NA	37.2	NA	(10)
Huang *et al* (n=41)	63.0	5.0	25.0	NA	(13)
Chen *et al* (n=29)	69.0	17.0	21.0	NA	(26)
Liu *et al* (n=12)	54.5	8.3	0.0	NA	(21)
Chan *et al* (n=6)	NA	28.6	28.6	66.7	(27)

NA, not applicable.

activated T cells and macrophages (57-59). Cells continue to be activated and expand, releasing inflammatory mediators; however, the overwhelming release of inflammatory factors not only recruits more immune cells, but also damages the homeostasis of the immune system and the function of normal cells, resulting in a cytokine storm (57-59).

Direct virus infection and uncontrolled inflammation can cause damage to the microvascular system, destroying the integrity of the vascular EC barrier, and resulting in the reduction of platelet EC adhesion molecule-1 (PECAM-1) on the cell surface and an increase in plasma soluble PECAM-1 (60,61). Moreover, EC damage may lead to the overexpression of tissue factor (TF), thereby activating the exogenous coagulation system, while inhibiting anticoagulation and fibrinolysis, among other processes, leading to DIC (50). The excessive inflammatory response in DIC and the destruction of the EC barrier promote each other, forming a feedback loop, which may eventually lead to systemic microvascular thrombosis, increased platelet consumption, massive consumption of coagulation factors and secondary hyperfibrinolysis, manifested as microcirculation disorders and bleeding (50). Moreover, IL-6 has an important role in the network of inflammatory mediators. It can cause coagulation disorders through various pathways, such as stimulating the liver to synthesize more thrombopoietin and fibrinogen, among others, and upregulating the expression of VEGF to destroy the stability of the vascular barrier, which stimulates monocytes to express more tissue factors and exacerbates activation of the exogenous coagulation system (50,58). The generated thrombin in turn can induce vascular endothelium to produce more IL-6 and other cytokines. Storms and coagulation disorders thus form a vicious circle (50,58).

Liver damage. Increased levels of glutamic-pyruvic transaminase and glutamic oxaloacetic transaminase, and decreased levels of albumin, have been detected in patients with COVID-19 (13,14). These findings suggest the development of liver dysfunction induced by SARS-CoV-2 and a reduction in the synthesis of clotting factors, ultimately causing coagulation disorders. Moreover, coagulation dysfunction can be caused by the use of antiviral drugs, such as ribavirin, which is associated with hepatotoxicity, and the reduced synthesis of coagulation factors and other molecules (50,62).

Ischemic hypoxic reperfusion injury or attack of ECs by SARS-CoV-2. Ischemic hypoxic reperfusion injury can trigger oxidative stress in ECs, thus increasing the production of superoxide and decreasing the production of nitric oxide. This results in EC damage, exposure of TF on the outer membrane of vascular cells and the activation of exogenous coagulation pathways (50). SARS-CoV-2 may also aggravate damage to ECs by directly binding to ACE2 on their surfaces. The expression of TF on the cell surface increases upon EC damage. This causes damage to antithrombin III, TF pathway inhibitor and protein C, as well as the loss of anticoagulant properties. EC damage also leads to an imbalance in fibrinolysis, resulting in coagulation dysfunction (50).

Cardiopulmonary bypass pipes and improper use of blood products have also been reported to cause abnormal coagulation (50). Coagulation disorders can appear at any stage of COVID-19 and can worsen with disease progression. Therefore, the timely monitoring of blood coagulation may help improve treatment and prognosis for patients with COVID-19.

5. Potential treatments

The treatment strategies currently used for COVID-19 include providing oxygen, mechanical ventilation, intravenous antibiotics, antiviral drugs and some traditional Chinese medicines. Patients with severe infection and symptoms are subjected to mechanical ventilation; however, the efficacy of non-invasive ventilation is limited due to the development of hypoxia in patients with COVID-19 (14,50). Therefore, the transfusion of plasma from convalescent patients, blood-purifying therapy and immune therapy may help treat severe or critical patients.

Chloroquine is a widely used antimalarial drug, which has been reported to have potential therapeutic effects on various viral diseases (such as HIV-1/AIDS and SARS) (63,64). Chloroquine blocks viral infections by increasing endosomal pH, interfering with virus/cell binding and interfering with the glycosylation of SARS-CoV cell receptors (65). Wang *et al* (66) reported chloroquine to be highly effective

in the control of SARS-CoV-2 infection *in vitro*. Moreover, Gao *et al* (67) conducted clinical trials on 100 patients with COVID-19 infection. The results suggested that chloroquine had a significant effect in terms of viral clearance and clinical outcomes compared with those in the control groups. Therefore, the use of chloroquine may improve the prognosis of patients with COVID-19 and could be considered an effective treatment.

Hydroxychloroquine and chloroquine have similar chemical structures and cellular mechanisms of action (68). Gautret *et al* (69) performed a clinical trial study and indicated that hydroxychloroquine was associated with viral decrease and disappearance in patients with COVID-19. Moreover, Zhou *et al* (70) demonstrated that hydroxychloroquine may provide better results than chloroquine for the treatment of SARS-CoV-2 infection. Indeed, hydroxychloroquine can attenuate the severe progression of COVID-19, inhibiting the cytokine storm by suppressing T cell activation. In addition, it has fewer side effects and is safe in pregnancy . Based on these findings, it was hypothesized that hydroxychloroquine may be more effective than chloroquine in treating patients with COVID-19.

Radecivir has a structure similar to adenosine and exhibits broad-spectrum antiviral activity against RNA viruses (71). Notably, it has been reported to have antiviral activity against various CoVs, including SARS-CoV and MERS-CoV, *in vitro* and *in vivo* (72,73). Radecivir has been reported to lead to the premature termination of viral RNA chains by inhibiting RNA-dependent RNA polymerase, consequently halting replication of the viral genome (74). In a recent *in vitro* study, remdesivir was found to effectively inhibit SARS-CoV-2 (67). Moreover, the first case report of a patient with COVID-19 in the USA indicated that the use of redoxivir could improve their condition (increased oxygen saturation values, improved appetite and reduced cough symptoms) (75). Remdesivir is currently undergoing multiple trials in different countries, including two randomized phase III trials in China (NCT04252664 and NCT04257656).

Glycyrrhizic acid and MSCs have immunoregulatory and anti-inflammatory functions (76-78). The antiviral activity of ribavirin, 6-azapyrimidine, pyrazolofuran, mycophenolic acid and glycyrrhizin has been shown based on two clinically isolated CoVs (FFM-1 and FFM-2) from patients with SARS included in the Frankfurt University Clinical Center (79). Glycyrrhizin has been reported to be more efficient in inhibiting the replication of SARS-associated viruses, compared with ribavirin, 6-azauridine, pyrazofurin and mycophenolic acid (79). Furthermore, a clinical trial revealed that MSCs may have significant effects on COVID-19, such as decreasing CRP levels, improving lung symptoms and significantly improving lymphopenia (80). Therefore, glycyrrhizic acid and MSCs may prevent or reduce excessive cytokine storms and improve prognosis in patients with COVID-19.

In addition, a clinical trial revealed that ruxolitinib could improve clinical symptoms by reducing cytokine storms (81). Notably, it is clear that there are currently no drugs available that specifically target SARS-CoV-2. The primary focus is on symptomatic treatment and preventing complications. In addition, the diagnosis and treatment of COVID-19 during its early stages may significantly reduce mortality.

6. Conclusions

In conclusion, COVID-19 causes lung damage and multiple systemic changes in patients, especially in the hematological system. In the early stages, patients present with lymphopenia. Patients develop thrombocytopenia, coagulation disorders and CRS in the later stage of disease, which can lead to DIC and multiple organ failure. Thus, hematological changes are of critical importance for patients with COVID-19. However, the relevant mechanisms are still unclear. Based on the existing clinical findings and the experience during SARS, research on the underlying mechanisms may help to improve the diagnosis, treatment and prognosis of patients with COVID-19.

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Authors' contributions

JY, YJ, YZ, MY wrote the manuscript. ZL designed Table I and XZ designed Table II. HD collected relevant literature. JY and MY revised and commented on the mansucript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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