Hematological manifestations and complications of COVID-19

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Abstract

The virus SARS-CoV-2 commonly causes self-resolving, flu-like illnesses in the majority of patients, but a critical illness can be seen in 5% of cases — especially in the elderly population or in patients with multiple comorbidities. When COVID-19 is severe, it can cause pneumonia and hypoxemic respiratory failure, and can progress to viremia involving multiple organ systems. It causes significant cytopenia, mainly severe lymphopenia, and excessive exhaustion of CD8+ T cells, resulting in an immunocompromised state and cytokine storm. Furthermore, COVID-19 can commonly be complicated with acute thrombotic events, including venous thromboembolism, acute stroke, acute myocardial infarction, clotting of hemodialysis and extracorporeal membrane oxygenation (ECMO) catheters, and acute limb ischemia. This makes SARS-COV-2 a unique virus with an undiscovered pathophysiology. Therefore, patients with COVID-19 need close monitoring of their symptoms and laboratory parameters, and early hospitalization and treatment in severe cases. Early identification of severe cases and the abovementioned complications of COVID-19 could decrease the morbidity and mortality caused by the disease. In the study, we summarize what is currently known about the hematological manifestations and complications of COVID-19.

Key words: COVID-19, lymphopenia, cytokine storm, thromboembolism, hypercoagulable state
Introduction and background

The coronavirus disease from 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 16 million people and killed more than 650,000 around the world.\(^1\) It was first identified in Wuhan, China at the end of 2019 and rapidly spread, resulting in a pandemic. Coronaviruses are enveloped RNA viruses which commonly cause cold-like illnesses in immunocompetent hosts.\(^3\) It has a similar receptor binding structure to that of the SARS-CoV virus and uses angiotensin-converting enzyme 2 (ACE2) to enter the host cells.\(^4\) SARS-CoV-2 is mainly transmitted person to person via close contact or droplets with an incubation period – on average 5 days prior to symptoms appearing.\(^5\) It causes life-threatening disease in 5% of cases, especially in the elderly and in patients with multiple coexisting medical conditions; it has a mortality rate of 2.3%\(^6\). Previously detected strains, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are zoonotic viruses which caused outbreaks in China and the Middle East, respectively. However, they did not result in a pandemic such as SARS-CoV-2 has.\(^7\)–\(^9\) COVID-19 primarily manifests as a respiratory tract infection causing hypoxemic respiratory failure. However, there is an enormous amount of data published almost daily demonstrating that it may involve multiple organ systems, including the nervous, cardiovascular, respiratory, gastrointestinal, renal, hematopoietic, and immune systems. This article summarizes the hematological manifestations and complications of COVID-19.

Alterations in cell counts in COVID-19

One of the first hematological manifestations of COVID-19 to be noticed was alterations in cell lineages, lymphopenia being the most prominent finding. A summary of studies examining cell lineage alterations in COVID-19 is presented in Table 1. A retrospective observation of 7,736 patients in China during the first 2 months of the pandemic outbreak compared the clinical characteristics of patients between severe and non-severe cases.\(^10\) Guan et al. found that the majority of the patients had low blood counts across all lineages, which were more prominent in patients with a severe form of the disease.\(^10\) On admission, lymphopenia was present in 83.2% of the patients, thrombocytopenia in 36.2% and leukopenia in 33.7%. Lymphopenia was the most commonly seen abnormally in blood counts, being present in 96% of the severe cases and 80% of the non-severe cases. The median hemoglobin level was found to be lower in severe cases than in non-severe cases (12.8 g/dL and 13.5 g/dL, respectively). In addition, thrombocytopenia was seen in 57.7% of the severe cases and in 31.6% of the non-severe cases. Other observational studies from China with fewer patients (41, 99, 138, and 201) reported similar results on patients with COVID-19: lymphopenia was evident in all studies and was more commonly seen in severe cases.\(^11\)–\(^13\) A retrospective cohort study with 201 patients from Wuhan focused on a comparison of patients with acute respiratory distress syndrome (ARDS) with those without ARDS. They found that the patients with ARDS had significantly lower lymphocyte counts and CD-8 T-cell counts. The study also showed that patients with neutrophilia had an increased risk of mortality.\(^13\) This might be secondary to the disease course becoming complicated by bacterial superinfection. Further studies from other countries

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<tbody>
<tr>
<td>Guan et al.(^10)</td>
<td>1099 hospitalized patients</td>
<td>4700</td>
<td>33.7%</td>
<td>1000</td>
<td>83.2%</td>
<td>13.4</td>
<td>168</td>
<td>36.2%</td>
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<tr>
<td>Wu et al.(^13)</td>
<td>201 hospitalized patients</td>
<td>5940</td>
<td>N/A</td>
<td>910</td>
<td>64%</td>
<td>N/A</td>
<td>180</td>
<td>N/A</td>
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<tr>
<td>Zhou et al.(^28)</td>
<td>191 hospitalized patients</td>
<td>6200</td>
<td>17%</td>
<td>1000</td>
<td>40%</td>
<td>12.8</td>
<td>206</td>
<td>7%</td>
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<tr>
<td>Wang et al.(^27)</td>
<td>138 hospitalized patients</td>
<td>4500</td>
<td>N/A</td>
<td>800</td>
<td>70.3%</td>
<td>N/A</td>
<td>163</td>
<td>N/A</td>
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<tr>
<td>Fan et al.(^15)</td>
<td>67 hospitalized patients</td>
<td>4700</td>
<td>29.2%</td>
<td>1200</td>
<td>36.9%</td>
<td>14</td>
<td>201</td>
<td>20%</td>
</tr>
<tr>
<td>Huang et al.(^11)</td>
<td>41 hospitalized patients</td>
<td>6200</td>
<td>25%</td>
<td>800</td>
<td>63%</td>
<td>12.6</td>
<td>164</td>
<td>5%</td>
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<tr>
<td>Young et al.(^14)</td>
<td>18 hospitalized patients</td>
<td>4600</td>
<td>N/A</td>
<td>1200</td>
<td>39%</td>
<td>13.5</td>
<td>159</td>
<td>N/A</td>
</tr>
</tbody>
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WBC – white blood cell; ALC – absolute lymphocyte count; Hgb – hemoglobin.
that analyzed the effects of SARS-CoV-2 infection on cell counts have shown similar results. A descriptive case series from Singapore on 18 hospitalized patients reported that 39% of the patients had lymphopenia. The majority of their patients had a mild form of the disease and 66% of them did not require supplemental oxygen, which is most likely explained by the low rate of lymphopenia among them.\textsuperscript{14} Another retrospective observational study on 69 patients from the National Center for Infectious Diseases (NCID) in Singapore focused on the hematological parameters of COVID-19 patients.\textsuperscript{15} They observed that 29% of the patients presented with severe leukopenia (WBC < 2 x 10^9/L); also, 36.9% of the patients presented with lymphopenia and 5 out of 25 had severe lymphopenia (ALC < 0.5 x 10^9/L). Lymphopenia was more profound in intensive care unit (ICU) patients, with 7 out of 9 being lymphopenic, 4 of whom had severe lymphopenia. In addition, 20% of their patients had mild thrombocytopenia (platelet count 100–150 x 10^9/L).

Peripheral blood smears obtained from 69% of the patients showed a few reactive lymphocytes, of which a subset appeared lymphoplasmacytoid. This is contrary to the experience with the SARS-CoV outbreak in 2003, where reactive lymphocytes were not observed in a study from Singapore on hematological parameters and were observed in only 15% of cases in a study from Hong Kong.\textsuperscript{16,17} Lymphopenia is a well-known feature of SARS-CoV, and was described in patients in Hong Kong and Singapore afflicted with the disease in 2003. It was associated with poor prognosis and ICU stay.\textsuperscript{16–18} Monitoring hematological parameters might help physicians to decide which patients need to be admitted to the ICU. Fan et al. recommended that severe lymphopenia <0.6 x 10^9/L should be considered as one of the indicators for early admission for supportive care in the ICU.\textsuperscript{15} Their ICU patients also developed more prominent, statistically significant decreases in their hemoglobin levels, absolute lymphocyte count (ALC) and absolute monocyte count (AMC), and increases in absolute neutrophil count (ANC), as compared to the non-ICU group. Fan et al. also performed flow cytometry (FCM) on the peripheral blood of patients in the ICU who had prominent lymphopenia. They found that the ICU patients had significantly lower CD45+, CD3+, CD4+, CD8+, CD19+, and CD16/56+ counts. Inversion of the CD4/CD8 ratio is commonly seen in viral infections such as the human immunodeficiency virus (HIV) and cytomegalovirus (CMV). However, the CD4/CD8 ratio was not inverted in all groups of patients.

Lymphopenia caused by COVID-19 and its detrimental effects on the immune system have been further analyzed. Zheng et al. studied the immunological characteristics of peripheral blood leukocytes from 16 patients in Kunming, China and found that COVID-19 damages the functioning of CD4+ T cells and promotes the excessive activation and possibly the subsequent exhaustion of CD8+ T cells.\textsuperscript{19} A proposed mechanism has been illustrated in Fig. 1. This phenomenon was also previously observed in some chronic infections such as HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as in cancer; it can eventually diminish the host’s antiviral immunity.\textsuperscript{20} Previous studies indicated that multi-functional T cells play an important role in immunity against HIV infection and immunity after vaccination. Therefore, functional damage to CD4+ T cells may have predisposed COVID-19 patients to severe disease.\textsuperscript{21} According to Zheng et al., patients with severe SARS-CoV-2 infection had fewer of the non-exhausted (PD-1-negative, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-negative and T-cell immunoreceptor with Ig and ITIM domains (TIGIT)-negative CD8+ T cells than the healthy control and mild disease course groups.\textsuperscript{19} For CD8+ T cells, it is beneficial to have a functional blockade of PD-1, CTLA-4 and TIGIT to maintain their antigen-specific immunity and antiviral effects.\textsuperscript{22,23} Therefore, the excessive exhaustion of CD8+ T cells in severe patients may reduce patients’ cellular immune response to SARS-CoV-2. A cohort study of 452 patients was performed by Qin et al. in Wuhan, China and showed the dysregulation of immune response in patients with COVID-19.\textsuperscript{24} They found that severe cases had higher leukocyte and neutrophil counts, lower lymphocyte counts, higher neutrophil-to-lymphocyte ratio, and lower percentages of monocytes, eosinophils and basophils. In addition, a lymphocyte subset analysis in 44 patients with COVID-19 revealed a decreased number of B cells, T cells and natural killer (NK) cells, which was more evident in the severe cases (743.6/μL compared to 1020.1/μL; p = 0.032) as compared with the non-severe group. The T-cell counts were found to have decreased to nearly half the lower limit of normal, indicating that T cells were more affected by SARS-CoV-2, especially

\begin{figure}[h]
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\caption{Exhaustion of CD8+ T cells in SARS-CoV-2 infection.\textsuperscript{19,20} T cells express cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1) inhibitory receptors which are activated by chronic infections. PD-1 signaling decreases Akt (protein kinase B) and mammalian target of rapamycin (mTOR) activity, which switches T-cell metabolism from glycolysis to fatty acid oxidation, resulting in mitochondrial depolarization, a higher rate of ROS production and functional impairment of T cells.}
\end{figure}
Hypercoagulable state and acute thrombotic events in COVID-19

COVID-19 is a novel disease with a very broad spectrum of complications involving different organ systems that are mainly caused by a hypercoagulable state. Patients with severe SARS-CoV-2 infection become prone to develop coagulation abnormalities and acute thrombotic events, but the pathogenesis of hypercoagulopathy in COVID-19 is not completely understood. Direct endothelial injury by SARS-CoV-2, immobilization due to severe illness, and a hypercoagulable state caused by increased inflammation and circulating prothrombotic factors are among the reasons why patients with COVID-19 have such a high tendency to develop acute thrombotic events. High d-dimer levels have been reported to be associated with the severe form of disease; as d-dimer is a fibrin degradation product, this indicates thrombin generation and fibrin dissolution. A multicenter retrospective analysis on 1,099 patients from China showed that 46.4% of patients with SARS-CoV-2 infection had elevated d-dimer levels. D-dimer elevation was more prominently seen in patients with severe COVID-19 compared to non-severe cases (59.6% compared with 43.2%). There are additional studies supporting the evidence that an elevated d-dimer level is associated with adverse outcomes and higher mortality.

Panigada et al. studied coagulation parameters and other assays, including von Willebrand factor (VWF) and thromboelastography (TEG), on 24 patients in the ICU who had COVID-19. They also found that the patients were in a hypercoagulable state. The patients had normal-to-increased platelet counts, near-normal prothrombin time (PT) and activated partial thromboplastin time (aPTT), increased fibrinogen and dramatically increased d-dimer levels, increased factor VIII and VWF levels, decreased antithrombin levels, and increased protein C levels. There are similar studies supporting these findings.

Severely ill COVID-19 patients might have similar laboratory findings, with patients suffering from disseminated intravascular coagulation (DIC) who meet the criteria for probable DIC in the scoring system published by the International Society on Thrombosis and Hemostasis (ISTH) in 2009. However, the majority of acutely ill patients with COVID-19 develop thrombosis rather than bleeding, which later is commonly seen in DIC. As explained previously, patients with COVID-19 have high fibrinogen and factor VIII activity, which suggests that a significant consumption of coagulation factors is not seen as it is in DIC. An observational study during treatment was an independent influencing factor for prolonged hospitalization. It was suggested that markedly elevated platelet counts and longer average hospitalization may be related to the cytokine storm.
Inflammatory markers and cytokine storm in COVID-19

SARS-CoV-2 infection may cause a very broad spectrum of the COVID-19 disease, from asymptomatic (up to 40–45% of all cases), through mild (81% of the symptomatic cases) and severe (14% of the symptomatic cases), to life-threatening infections (5% of the symptomatic cases).6,47 Its mean incubation period is 5 days, ranging from 1 to 14 days.48 During the incubation period, it can present with fever, malaise, sore throat, diarrhea, and other non-specific symptoms.19 During this period, peripheral blood leukocytes and lymphocytes are usually not significantly reduced.49 In the 2nd phase of the disease, usually occurring 7–14 days after the disease onset, the virus can cause viremia which mainly affects the lungs, gastrointestinal tract and heart by binding to ACE-2 receptors.50 In this phase, pneumonia worsens the disease course by causing diffuse bilateral patchy infiltrates in the lungs and potentially causing hypoxemic respiratory failure. As explained previously, lymphocyte counts are significantly lower in severe cases and inflammatory markers (e.g., ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate), elevated aminotransaminase (ALT/AST) levels and lactate dehydrogenase (LDH) levels can be detected in the blood in high amounts.10 Patients might also have markedly elevated levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, monocyte chemotactractant protein-1 (MCP-1), and macrophage inflammatory protein 1-a (MIP1-a) and tumor necrosis factor α (TNF-α) if they go into a state of “cytokine storm,” which may induce lymphocyte apoptosis.51,52 Cytokine release syndrome (CRS) or cytokine storm is a type of acute systemic inflammatory reaction classically presenting with fever and multiple organ dysfunction. It commonly occurs secondary to immunotherapies (chimeric antigen receptor T-cell therapy or therapeutic antibodies) and haploidentical allogeneic transplantation. However, severe viral infections such as influenza or SARS-CoV-2 can also cause severe inflammatory response and cytokine storm.53–58 Mild cases of CRS are treated with antiinflammatories, antipyretics and intravenous fluids. Intravenous steroids and tocilizumab (an IL-6 receptor antagonist) can be used for severe cases.55

Conclusions

SARS-CoV-2 is a novel virus which can cause significant changes in blood counts, mainly causing severe lymphopenia and excessive exhaustion of CD8+ T cells in severe cases, which may reduce patients’ cellular immune response. When COVID-19 results in viremia in the later course of the disease, it can cause severe inflammatory reactions similar to cytokine storm, which might require ICU admission. In addition, acute thrombotic events are...
commonly seen in patients with severe COVID-19, which makes SARS-COV-2 a unique virus with undiscovered pathophysiology. Patients who are infected with the virus should be evaluated carefully by checking complete blood counts and inflammatory markers as well as further studies to diagnose acute thrombotic events in high-risk or symptomatic cases, both at baseline and during the disease course. Early identification of severe cases and the complications of COVID-19 could decrease the morbidity and mortality rates associated with this disease.

**References**


