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# Alterations of Hematological Profile in Patients with SARS-CoV-2 Infection: An Overview

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REVIEW

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# Alterations of Hematological Profile in Patients with SARS-CoV-2 Infection: An Overview

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**Abstract**

**The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in the coronavirus disease 2019 (COVID-19) is now prevalent around the world and has been accountable for a significant number of fatalities and disability. An extensive summary of the changes in hematological profiles seen in COVID-19-infected patients is given in this review.**

**The symptoms of COVID-19 range from moderate or undetectable to life-threatening respiratory distress and multiple organ dysfunction. The importance of hematological discrepancies as biomarkers of illness degree of severity, clinical course, and outcome becoming increasingly appreciated. Increased neutrophils, reduced lymphocytes, and raised C-reactive protein are typical initial laboratory findings.**

**Elevated D-Dimer levels are linked to dysfunctional coagulation such as disseminated intravascular coagulation (DIC), which can predict mortality and represent the severity of the condition. In severe cases, anemia of inflammation is common, with reduced hemoglobin and high ferritin.**

**Prognostication is aided by biochemical markers such as erythrocyte sedimentation rate (ESR), ferritin, and C-reactive protein. Blood group types may also affect a human being's susceptibility to infection.**

**Real-time "reverse transcription polymerase chain reaction (RT-PCR) and serology tests are the mainstays of diagnostic testing in laboratories. Low-molecular-weight heparin anticoagulant prophylaxis is advised to reduce thrombotic consequences, taking into account the distinctive characteristics of each patient.**

**In conclusion, accurate diagnosis, risk identification, and therapeutic intervention of afflicted persons depend on an awareness of the hematological symptoms of COVID-19. It is necessary to conduct additional studies to clarify the underlying mechanisms and improve treatment approaches in this dynamic COVID-19 pandemic environment.**

***Keywords:*** COVID-19, SARS-CoV-2, Anemia, Thrombocytopenia

## 1. Introduction

The coronavirus, commonly referred to as COVID-19, is an extremely infectious viruses that was first identified in China in December 2019. Of the 541 million instances that have been identified with COVID-19, approximately 6 million cases have died from the illness. On March 11, 2020, the (WHO) World Health Organization designated this infection to be a pandemic [1].

Numerous COVID-19 strains have been reported worldwide thus far, and new strains are being discovered every day [2]. Genetically identical to both SARS-CoV ("Severe Acute Respiratory Syndrome Virus") and MERS-CoV ("Middle East Respiratory Syndrome coronavirus"), the coronavirus is a member of the beta coronavirus family of SARS-Cov-2 [3]. Almost eighty percent of COVID-19 patients either have no symptoms at all or only minor symptoms that go away on their own or with supportive treatment, preventing

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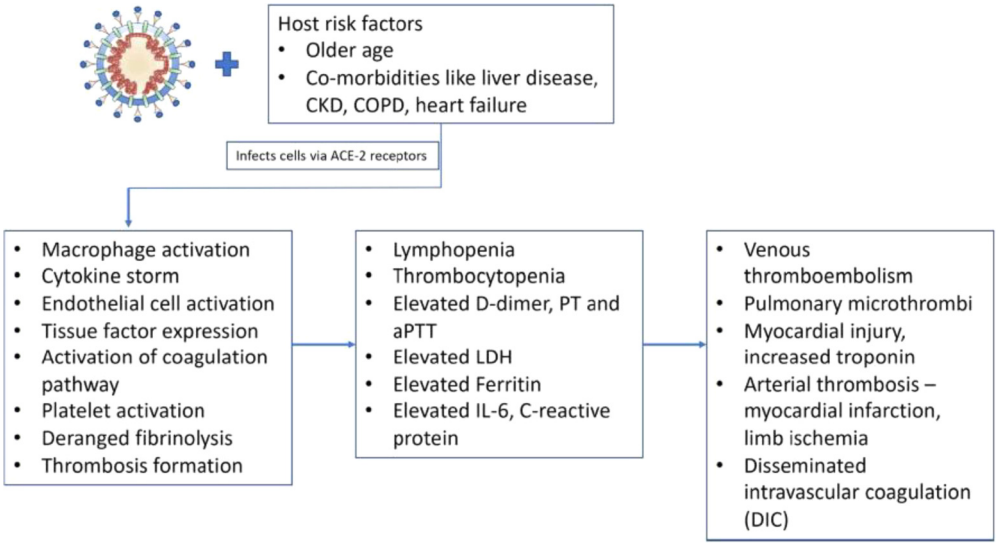


*Fig. 1. Hematological manifestations of SARS-CoV-2 infection.*

complications or hospital stays. Fever, cough, nausea, vomiting, exhaustion, and shortness of breath are the most prevalent symptomatic presentations of COVID-19 disease in subjects who have been confirmed to carry the virus; however, other research suggests that high temperature is less prevalent in SARS-CoV-2 than in MERS-CoV and SARS-CoV. In contrast to adults (aged 15 to 64), children under the age of 14 have a lower risk of contracting COVID-19 infection; nevertheless, individuals over 65 have a higher risk of contracting this infection [4].

According to laboratory examination, the initial hematological snapshot of the COVID-19 virus showed an increase in neutrophils, a decline in lymphocytes, and an upsurge in C-reactive protein. In the early stages of the illness, each of these laboratory measures was thought to be a predictor of death [5]. Along with thrombocytopenia and leukopenia, lymphopenia—characterized by decreased numbers of CD4 and CD8 T-lymphocyte cells—is a common hematologic feature in patients with COVID-19. These T-lymphocytes are a fundamental component of body immunity, aiding in the individual's battle against viruses and their removal from the body. As a result, they serve as helpful indicators of disease severity and prognostic indicators for evaluating the clinical results of the illness [6] Fig. 1 [7].

Acute kidney impairment, myocardial infarction, muscular damage, gastrointestinal hemorrhage, and various overwhelmed secondary microbial infections (both bacterial and fungal) are the symptoms of a complicated COVID-19 infection [8]. Although polymerase chain reaction (PCR) molecular testing is used to diagnose COVID-19, hematological, radiological, and biochemical indicators also have a significant role in evaluating the disease's severity, clinical course, and prognosis. The two hematological assays that show hematological abnormalities related to COVID-19 are the coagulation profile and the whole blood count. In circumstances when the patient's clinical presentation is inconsistent and molecular testing is not accessible, several clinicians have identified hematological irregularities in SARS-CoV-2 as indications of the illness [9].

## 2. Hematological complications

### *2.1. Thrombocytopenia*

Individuals with advanced COVID-19 disease have more severe thrombocytopenia, which affects 5–21% of individuals. There have been reports of thrombotic thrombocytopenic events after COVID-19, mostly in older subjects (above 50 years) with moderate to severe illness [10, 11]. A possible explanation for the thrombocytopenia observed in COVID-19 cases is anomalous hemopoiesis (Fig. 2) [12]. Bone marrow cells are susceptible to infection by coronaviruses. Studies have demonstrated that the coronavirus "HCoV-229E" can infiltrate the cells of the bone marrow by attaching itself to host cell-expressed CD13, which causes apoptosis and growth suppression. Reduced platelet production and ultimately thrombocytopenia are the outcomes of this apoptosis. There is conjecture that the HCoV-229E antigen that binds the CD13 shares characteristics with antigens from COVID-19. Patients with SARS-CoV-2 similarly have thrombocytopenia as a result [13].

COVID-19 viral infection is also linked to immune-mediated thrombocytopenia, commonly known as

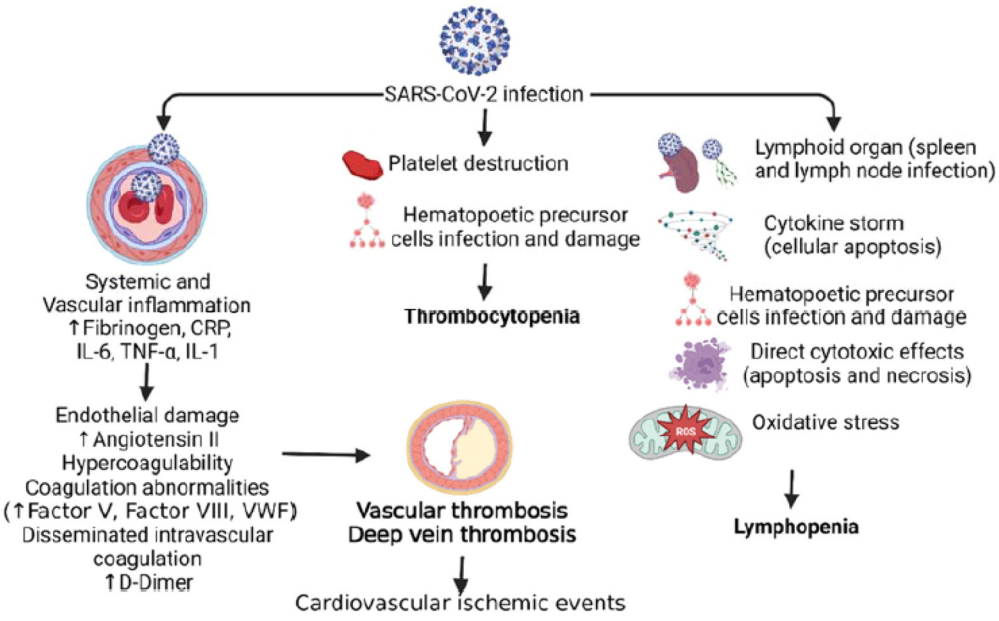


*Fig. 2. Pathophysiology of hematological disorders in SARS-CoV-2 infection.*

"immune thrombocytopenic purpura" (ITP), an acquired hemorrhagic diathesis of deficient production that affects males somewhat more frequently than females, with older men being more susceptible to the condition. This ITP can happen after receiving the COVID-19 immunization [14] (Fig. 2), although it typically happens 2–3 weeks after the beginning of COVID-19 manifestations [12].

### 2.2. Coagulation abnormalities

An extremely rare but dangerous systemic condition called disseminated intravascular coagulation (DIC) is characterized by consumption coagulopathy, fibrinolysis, and procoagulant effects that can be fatal [15]. Notably, several investigations have revealed that SARS-CoV-2 patients have high D-Dimer levels, a key indicator of DIC development. Elevated D-Dimers correlated with illness severity [16] as a result of increased severity and disease progression. This is a good predictor of in-hospital death.

Additionally, SARS-CoV-2 patients have six times greater thrombotic rates. Modified coagulation markers are not very good predictors of COVID-19 outcomes. Low fibrinogen count, extended PT, and low platelet count were other indicators. Additionally, it was noted that patients in various stages were more likely to exhibit hypercoagulability [17, 18].

Patients with COVID-19 are more susceptible to complicated events like deep vein thrombosis, pulmonary embolisms, and cardiac toxicity. Von Willebrand factor (vWF) and factor VIC, two significant, traditional indicators of coagulability, increased in the patients' laboratory indices during the later stages of the illness. Elevated D-dimers continued to be poor prognostic markers even after these laboratory indices fell with continuous anti-thrombin medication. Indicating coagulation and anemic problems, higher ferritin concentrations were also seen in SARS-CoV-2 patients [19, 20] (Fig. 2) [12].

### 2.3. Hemoglobin and red cells

Anemia of inflammation is proven to be the most prevalent kind among the primary anemia forms associated with COVID-19. Clinically speaking, anemia of chronic inflammation is described as serum ferritin of more than 100 µg/L and transferrin saturation of less than 20% [21]. Anemia is the result of impaired iron homeostasis caused by elevated ferritin, a significant iron storage protein, which is raised in response to inflammation. CRP has been confirmed to be significantly greater in anemic cases, and it is positively connected with ferritin levels. In addition, there was a rise in erythrocyte distribution width (RDW) and a reduction in hemoglobin in subjects with severe SARS-CoV-2. However, when these values were matched to individuals with less severe COVID-19, no significance was found [22].

Extensive inflammation in severe SARS-CoV-2 results in negative hematological impacts, including decreased hemoglobin rates; however, in mild to moderate COVID-19, no substantial variations in hemoglobin measures or hematocrit have been recorded [23].

### 2.4. White cells

Leukopenia affects 20–40% of SARS-CoV-2 patients, while leukocytosis affects 3%–24% of them. There is a substantial correlation between SARS-CoV-2 and lymphopenia. The second week of SARS-CoV-2 infection is marked by a recognizable rise in reactive cells and circulatory lymphocytes that release antibodies. 52.9% of patients have decreased eosinophils [24].

Notably, there is a positive association between lymphopenia and the disease severity. The discovery of blue-green intracytoplasmic inclusion bodies in the neutrophils and the monocytes on blood smears from SARS-CoV-2 patients is also intriguing. These results point to a dismal prognosis and have been previously noted in the setting of severe liver failure and lactic acidosis. Even though each of these findings is noteworthy in the context of COVID-19, more study is needed to fully appreciate the clinical significance of these morphological abnormalities [25].

Different processes are expected to be involved in the association between COVID-19 infection and CD4+ and CD8+ T cell lymphopenia. The angiotensin-converting enzyme-2 (ACE-2) receptors, which are frequently located in the lungs, heart, and elementary system, is the route by which the virus is known to assault human cells. Lymphocytes also have these receptors on their cell surface. The virus of SARS-CoV-2 may therefore directly attach to lymphocytes and induce cell lysis. Thus, lymphopenia could be a part of the cascade of inflammation. A decline in cytotoxic T lymphocytes (CTLs) and natural killer (NK), which are critical for controlling viral infections, causes the condition to worsen. A large percentage of SARS-CoV-2 patients—especially those with more severe illness—have been detected to have lymphopenia. Reduced numbers of NK cells, CTLs, memory T cells, and B lymphocytes are seen in severe illness [26].

The COVID-19-mediated immune dysregulation leads to the generation of neutrophils and the death of lymphocytes. Lymphopenia is linked to neutrophilia. Additionally, a subsequent bacterial infection—which is more common in people with severe disease—can result in neutrophilia. A recently postulated factor in the pathophysiology of COVID-19 is a function of neutrophils that is not as well characterized [27].

### 2.5. Other markers

In cases of progressive COVID-19 infection, several biochemical assays are suggested as possible prognostic markers. In complex viral infections, serum ferritin levels are raised in 74.2% of cases. Serum ferritin levels above normal in 63 COVID-19 patients increased the risk of "acute respiratory distress syndrome" (ARDS). Subjects with concomitant conditions such as thrombotic complications, diabetes, hepatic dysfunction, and malignancy had higher levels of ferritin [28].

In cases of severe COVID-19 infection, higher C-reactive protein (CRP) levels were seen in about 81.5% of cases, LDH in 58.1%, and pro-calcitonin in 13.7%. These findings were associated with subsequent bacterial infection. Furthermore, ESR was found to be significantly raised in multiple investigations and was thought to be a predictor of infection severity [29].

Numerous research has reported an association between COVID-19 and the ABO blood group. Blood types A and O may be more and less likely, respectively, to contract COVID-19, according to research of 31,100 pooled patients with the virus; however, there was no connection found between the blood ABO groups and the severity or mortality of the illness[30].

## 3. Laboratory diagnosis of the illness

The following techniques are utilized to inform laboratory diagnosis tests for COVID-19: SARS-CoV-2 antigen immune-chromatographic test in upper respiratory airways specimens; RT-PCR; blood serologic testing for SARS-CoV-2 (Anti-SARS-CoV-2 IgM and/or IgG,), using enzyme-linked immunosorbent assay (ELISA) [31].

When diagnosing symptomatic individuals during the acute phase, the preferred laboratory test for COVID-19 identification is the PCR, which is regarded as the gold standard in this context. The real-time diagnostic RNA from upper respiratory tract specimens, like sputum, tracheal aspirate, oropharyngeal swab/oropharyngeal, nasopharyngeal lavage, and sputum, is used in RT-PCR [32–33].

The sensitivity of serological methods is characteristically inferior to the molecular methods, and it is mostly used for retrospective analysis. The foundation of serological testing is the identification of certain immunoglobulins (IgA, IgM, and IgG) produced in response to COVID-19 or the virus's antigen. Once there are few molecular test options or if symptoms have been present for at least 14 days, serology may be used [33].

## 4. Management of hematological aberrations in COVID-19 infection

### 4.1. Platelets

Since advanced SARS-CoV-2 infection is the only condition that causes thrombocytopenia, treating this

feature is typically not necessary. ITP has been reported in a few COVID-19 case reports, and all of the patients' outcomes were positive[34], [35].

### 4.2. Coagulation and fibrinolytic system

As stated by the "International Society on Thrombosis and Hemostasis", in-patients should regularly receive thrombolytic prophylaxis with a suitable dose of low-molecular-weight heparin. Additionally, heparin's anti-inflammatory features are advantageous for SARS-CoV-2 subjects. The clinical severity of the illness and any associated organ damage should be taken into consideration when determining the appropriate anticoagulant type and dose. It was discovered that obese patients required higher dosages [36].

Patients with sepsis-induced coagulopathy (SIC) may benefit from treatment with a full dose of anticoagulation [37]. Heparin use has been demonstrated to lower death rates in cases with significantly elevated D-dimer measures or who fulfilled the SIC criteria. Critically ill COVID-19 individuals have been documented to have heparin resistance. Anti-factor Xa levels in these patients could be useful in directing treatment [38].

Since it would be challenging to closely monitor the international normalized ratio while in COVID-19 isolation, patients taking warfarin had better be switched to alternate anticoagulants, like heparin. Since it requires less frequent monitoring than unfractionated heparin, low molecular weight heparin (LMWH) is the better option. If the patients can tolerate oral ingestion, they may be switched to direct oral anticoagulants [37].

### 4.3. Red blood cells

Despite reports of anemia in certain individuals, no research has demonstrated that transfusion assistance for this indication alone can improve outcomes. Chelation therapy and transfusions should be prescribed as needed to individuals with hemoglobinopathies and SARS-CoV-2 [39].

### 4.4. White blood cells

Research has been conducted regarding the usage of corticosteroids to decrease the inflammation caused by COVID-19. It was shown that individuals who got 6 mg daily of dexamethasone for a maximum of 10 days had mortality rates that were reduced by 8–26%. There are numerous ongoing clinical studies investigating the application of mesenchymal stem cells (MSCs) as SARS-CoV-2 treatment. Within three to six days of receiving MSC treatment, patients' lymphocyte counts increased and their CRP, cytokine-secreting T cells, and natural killer cells decreased. However, there are two things to keep in mind: the expense of these treatments and the length of time required to receive treatment approval [40].

## 5. Conclusion

Worldwide, the COVID-19 pandemic has had a severe consequence, especially for people with weakened immune systems. Raised D-dimer and CRP serum concentrations, thrombocytopenia, and lymphopenia are the most common hematologic problems associated with SARS-CoV-2. These variations are much more noticeable in people with severe SARS-CoV-2 disease, which suggests that they could be a marker for people who necessitate critical care and hospitalization. Treating patients with hematological disorders requires careful thought, and coagulation issues require special attention. As new scientific data becomes available, rules must be continuously revised.

## Ethical issue

Not applicable.

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Nil.

## Conflicts of interest

None.

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