Narrative Review Article

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Coronavirus disease 2019: Morphological changes in peripheral blood cells

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Abstract:

INTRODUCTION: The impact of severe acute respiratory syndrome coronavirus 2 on global health has been considerable since its emergence. Clinical laboratories are crucial in the diagnosis, treatment, and prognosis of patients with coronavirus disease 2019 (COVID-19). The study aims to review the published literature on the abnormal morphological features found in the peripheral blood smears of patients with COVID-19.

MATERIALS AND METHODS: A nonsystematic narrative review was carried out, utilizing four databases to search for publications that presented qualitative alterations in the peripheral blood cells of individuals with COVID-19. Thirty-three studies published between January 2020 and July 2022 were ultimately included in the review.

RESULTS: The majority of the studies reviewed focused on qualitative changes, with peripheral blood cell shape identified as an indicator of post-COVID-19 syndrome severity. Plasmacytic cells were found to be a relatively specific marker for COVID-19, while fragmented neutrophils were identified as an extremely sensitive morphological marker. Activation of monocytes was a strong predictor of disease outcome, and platelet aggregates served as an indicator of disease progression.

CONCLUSIONS: The identification of morphological abnormalities in peripheral blood cells can aid in diagnosing and prognosticating COVID-19 patients. Daily complete blood count tests in hospitalized patients are crucial for identifying numerical and morphological irregularities that indicate poor clinical outcomes and disease progression.

Keywords:

Blood smear, coronavirus disease 2019, morphology, peripheral blood cells, severe acute respiratory syndrome coronavirus 2

Introduction

Since December 2019, significant outbreaks have occurred due to the novel coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was first identified in Wuhan, China, and soon became a global pandemic.[1,2] The virus continues to spread, and every new variant discovered poses a significant risk to health-care systems worldwide. The rapid increase in cases, higher death rates, and economic consequences of the pandemic make it an ongoing global challenge.

From no symptoms to severe manifestations such as pneumonia or acute respiratory distress syndrome, COVID-19 symptoms vary among patients and, in some cases, may even result in multiple organ failure, which can prove fatal.[3,4] Recent research indicates that analyzing the morphology of blood cells plays a critical role in hematology, enabling the identification and comprehension of diverse disorders.[5]

The light microscope is commonly employed to examine peripheral blood films and

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plays a critical role in assessing blood cell morphology. Numerous studies have utilized blood cell morphology as a simple yet effective method to examine blood samples from patients with abnormal blood counts.[6] Mina *et al*. noted that COVID-19 patients have normal or slightly reduced hemoglobin levels, and there are no indications of anemia or red blood cell (RBC) count abnormalities during the assessment.[7]

Clinical laboratories have played a crucial role in diagnosing COVID-19 by identifying morphological changes in patients.[8] Accurate diagnosis, treatment, and prediction of outcomes in SARS-Cov-2-infected patients would be challenging without these findings.[8] In most COVID-19 patients, the lymphocyte count was significantly lower, suggesting that the virus has a detrimental effect on lymphocytes.[9]

Initially, studies on COVID-19 focused mainly on its epidemiological, clinical, and radiological features, while morphological changes received less attention. However, as COVID-19 spread worldwide, researchers started investigating the disease from various perspectives. For example, Zini *et al*. (2020) found that the cytoplasmic granulation and nucleus of COVID-19 patients exhibited peculiar morphologies, and platelet count was sometimes altered. Additionally, disordered granulopoiesis can lead to irregular granulocyte numbers. The cytokine storm is a possible causal factor in these morphological changes.[8]

The study aimed to determine how COVID-19 affects the morphology of peripheral blood cells by analyzing existing research on the topic.

Materials and Methods

A nonsystematic narrative review was performed to identify published literature on morphological alterations in peripheral blood cells in patients with COVID-19. The search was performed on July 30, 2022, using keywords such as "COVID-19," "SARS-CoV-2," "morphology," "peripheral blood cells," and "blood smear" in four databases, namely Web of Science, PubMed, Google Scholar, and Scopus.

Initially, 73 publications were retrieved through the search, which were then screened based on their titles and abstracts to identify studies reporting morphological changes in the peripheral blood cells of patients diagnosed with COVID-19. Ultimately, 33 studies published between January 2020 and January 2022 were included in the review. The studies included in the review were selected based on their relevance to the topic of morphological abnormalities in peripheral blood smears seen in COVID-19 patients, and only those that reported morphological changes in peripheral blood cells of COVID-19 patients were included. We reviewed the full texts of the included studies and extracted and synthesized data to identify common morphological changes observed in COVID-19 patients. The findings were summarized and synthesized narratively.

Discussion

Morphological changes in white blood cells

According to studies, disordered granulopoiesis is often linked with cytokine storms, inflammation, and in some cases, bacterial superinfections.[10] In COVID-19 patients, left-shift myeloid series with immature promyelocytes and metamyelocytes were the most common morphological changes observed in peripheral smears.[11-16] Left shifts in myeloid cells indicate the early release of immature cells from the bone marrow in response to stress, which is a common feature of many viral and inflammatory diseases. Previously, left shifts in neutrophils, myelocytes, and neutrophils in combination with neutrophilia were associated with bacterial infections, but recent observations confirm that these changes are also present in COVID-19 infections.[17,18]

Studies have shown that COVID-19 peripheral blood films can exhibit different neutrophils with nuclei similar to those of a fetus with abnormal nuclei, as well as ring-shaped nuclei with various shapes.[8,11,13,14,19,20-22] Smudge cells were commonly found in COVID-19 patients' peripheral blood smears, and there is increasing evidence that they are particularly sensitive to COVID-19.[12,16,21,23,24] COVID-19 patients may have an increase in neutrophil fragility, which could be due to cytokine overactivation, and hypercoagulability caused by disseminated intravascular coagulopathy, a common complication in hospitalized COVID-19 patients.[25] Smudge cells were found in COVID-19 patients' peripheral blood smears and were considered a highly sensitive result that may be due to neutrophilia. One of the reasons for this condition is the failure of neutrophil extracellular traps.[11] While COVID-19 patients have not previously shown increased numbers of smudged neutrophils, the detection of circulating apoptotic cells indicates that there may be an additional phase of neutrophil degeneration.[8] Different studies also observed neutrophil apoptosis and preapoptotic granulocytes in circulation.[8,11,14] In addition, peripheral blood smears of COVID-19 patients showed dysplastic neutrophils and a leukoerythroblastic reaction.[15,22,26] The inhibitory effects of virus-infected cells' cytokines on hematopoiesis may cause myelodysplastic changes.[22] Severe symptoms were associated with dysplastic neutrophils, which may result in nuclear dysmorphia and cytoplasmic changes before diagnosis and treatment.[8] Furthermore, neutrophils tended to have scanty basophilic granular

cytoplasm.[8,15,19,27] Severe disease was linked to segmented neutrophilia with vacuolization and toxic granulations, and some patients had inclusions similar to Howell–Jolly bodies and pseudo-Pelger–Huet inclusions.[28] Blue-green cytoplasmic inclusions were found in deceased individuals' neutrophils, possibly caused by lipid-rich lipofuscin from necrotic liver cells.[29] Peripheral blood smears from patients with COVID-19 exhibit reactive morphological features including lymphoplasmacytic cells with eccentric nuclei, dark-blue basophilic cytoplasm, and a distinct paranuclear hof.[8,11,13,30-32] Plasma cells circulating in the blood and cells with plasmablastic features, which include immature nucleoli and chromatin, have also been documented.[14,31] In addition, rare reactive lymphocytes with a plasma cell shape and circulating plasma cells were found.[17] Some studies identified lymphocytes with enormous granules and vacuolation, ring nuclei, expanded nucleoplasm, and lymphocyte apoptosis, along with the development of cytoplasmic-pods monocytes with cytoplasmic vacuolization, active granules, and atomic blebbing.[19,20,28] The appearance of reactive lymphocytes, which were neither cancerous nor normal in appearance, was another notable observation in the peripheral blood smears. Atypical lymphocytes were present in almost all COVID-19-positive patients with abundant light-blue cytoplasm, cytoplasmic pods, vacuolation, nuclear blebbing, and enhanced granulation.[8,16,20,22,31-34] Natural killer cells, cytotoxic T-lymphocytes, and Mott-like lymphocytes were also found, as well as lymphocytes with extensive inclusions in the cytoplasm.[30] The presence of circulating plasma and plasmacytic cells is also thought to characterize COVID-19.[11] An increased proportion of large and atypical monocytes, which are not commonly seen in peripheral blood smears of healthy individuals, were observed in patients with COVID-19.[34] Peripheral blood smears showed an increase in pleomorphic and vacuolated monocytes and monocytes with various abnormal morphologies and cytoplasmic vacuolation.[13,14,19,20,22,26,28] Eosinophilia is common, but eosinophilic malformations affect only a small percentage of patients.[19,27,35] Fragmented neutrophils have been identified as highly sensitive morphological markers of COVID-19, but more studies are needed to clarify their role in COVID-19 pathogenesis.[11] The inflammatory response and viral impacts are reflected in changes in leukocyte morphology. The prognosis is great for patients with monocytes and activated macrophages.[23] A peripheral blood smear can serve as a screening tool while waiting for reverse transcription–polymerase chain reaction (PCR) results and can be used to modify treatment regimens.[24]

Morphological changes in red blood cells

Abnormalities in RBC morphology, such as stomatocytes and knizocytes, which are not commonly observed in other types of anemia, were found in peripheral blood smears of COVID-19 patients.[36] Severe COVID-19 infections were also found to be associated with increased oxidation of structural proteins and defective membrane lipid homeostasis, leading to RBC deformity and thromboembolic events.[37] RBCs in COVID-19 patients showed abnormalities in morphology such as anisocytosis, spherocytes, stomatocytes, knizocytes, and polychromasia, as well as numerous mushroom-shaped cells, suggesting a significant impact of SARS-CoV-2 on RBC physiology, and highlighting the crucial role of oxidative stress. The presence of pincer cells in COVID-19 patients suggests that oxidative stress may be responsible for the disease's etiology.[36,38] In patients with a milder form of anisopoikilocytosis, unusual erythrocyte morphologies, including "mushrooms" and spherocytes, were observed in peripheral blood smear staining. These unusual RBCs are also found in bone marrow myelofibrosis and nonspecific dyserythropoiesis but only dispersed within a recognizable poikilocytosis in those cases. Mushroom-shaped erythrocytes showing irregularities in the membrane protein were also observed.[39] Rouleaux formations and autoagglutination were observed in some patients, which is thought to be caused by an increase in immune globulins and fibrinogen during viral infections.[40] In addition, spherocytes and schistocytes were observed in COVID-19 patients with vascular thrombosis and microangiopathy, indicating hemolytic processes.[41] COVID-19 microangiopathy may cause RBC injury through immune-mediated mechanisms or physical effects. In COVID-19 patients, biconcavity and complement activation were absent, leading to RBC stacking and agglutination, potentially resulting in microvascular thrombosis.[36] Circulating erythroblasts and red cell fragments have also been observed in peripheral blood films, along with nucleated cells, basophilic stippling, normocytic, and normochromic RBCs.[12,13,15] Leukoerythroblastic features were observed in a peripheral blood smear, along with normocytic anemia, rare nucleated red cells, coarse basophilic stippling, mild anisocytosis, and a few dacrocytes.[12,14] Additional research is required to establish the contribution of RBCs in the pathophysiology of COVID-19 infection, and potential strategies to reverse RBC dysfunction, such as minimizing the production of reactive oxygen species or utilizing antioxidants, should be explored.

Morphological changes in platelets

Chen *et al*. (2020) found that COVID-19 patients with delayed-phase thrombocytopenia experienced delayed-onset thrombocytopenia. An examination of the bone marrow aspiration of these patients showed inadequate maturation of megakaryocytes, resulting in a smaller proportion of platelet-producing

megakaryocytes.[42] A study conducted on various patients in intensive care units (ICUs) revealed that despite thrombocytopenia being a common finding in severe COVID-19 patients, the presence of platelet aggregates and macrothrombocytes in peripheral blood smears suggests increased platelet activity. The results were compared to those of individuals without COVID-19, in which the findings were entirely absent. The study suggested that this platelet morphology may be associated with severe COVID-19 infections. It has been recommended that the role of platelets should be correlated with COVID-19 patients who have thrombotic complications or respiratory failures.[43] Several studies have identified abnormalities in peripheral blood cells from COVID-19 patients, revealing the presence of large platelets in peripheral blood.[11,12,14-16,21,22,26] Zini *et al*. also discovered large vacuolated platelets in peripheral blood smears, and platelet satellitism was also seen.[8,21] Platelets that are larger than a regular RBC are referred to as "giant platelets." Patients with myelophthisis or myeloproliferative disorders usually have massive platelets. They are also the most common symptom of Bernard–Soulier syndrome.[18] Numerous studies have found COVID-19 giant platelets with dysmorphic characteristics, such as hyperchromatic granulomeres, peripheral clear patches of varying sizes, and pseudopod-like protrusions.[8,16,35,44] Another study on COVID-19 patients analyzed blood platelet indices to assess platelet morphology in hospitalized patients. The study found that platelet activity is increased in severe COVID-19 patients despite thrombocytopenia being a common finding. The presence of platelet aggregates and macrothrombocytes in peripheral blood smears indicated this increase. The study also identified clinical risk factors and biomarkers associated with platelet size, number, and maturity, indicating a connection with critical stages of COVID-19 patients. The study evaluated the lung tissue, bone marrow, and peripheral blood to screen for signs of COVID-19.[45] Table 1 shows more details. Although platelet counts are relatively normal in severe COVID-19 patients, blood film appearances suggest that platelets play a significant role in the disease process. Platelet aggregates may serve as a useful indicator of worsening disease.

Peripheral blood cell changes in coronavirus disease 2019 patients: The intersection of quantity and quality

COVID-19 patients often exhibit quantitative changes in peripheral blood cells that correspond to qualitative morphologic changes. Leukopenia is commonly associated with a left-shift myeloid series characterized by immature promyelocytes and metamyelocytes in neutrophils,[8] which indicates bone marrow hyperplasia and an increase in immature granulocytes due to the body's response to the infection. Likewise, lymphopenia often involves activated or atypical lymphocytes, indicating a reactive lymphocyte population that is responding to the viral infection.[46] Anisocytosis, spherocytes, stomatocytes, knizocytes, and polychromasia in RBCs are frequently associated with a decrease in RBC count and an increase in circulating erythroblasts and red cell fragments, indicating a response to inflammation and increased oxygen delivery demands.[9] Thrombocytopenia often involves large vacuolated platelets, platelet aggregates, varying sizes of platelets, and pseudopod-like protrusions, which are thought to be related to the inflammatory response and associated endothelial damage.[47] However, these associations are not absolute and may vary among individuals due to other factors such as medication use, comorbidities, and individual immune response. As such, a comprehensive evaluation of both quantitative and qualitative changes in peripheral blood cells is crucial for proper diagnosis and management of COVID-19 patients. The most common changes observed in the blood cells of COVID-19 patients during our clinical practice include

Table 1: Morphological changes in peripheral blood cells in coronavirus disease 2019 patients

Cell line	Changes observed	Reference(s)
Neutrophil	Left-shift myeloid series with immature promyelocytes and metamyelocytes, smudge cells, vacuolization and toxic granulations, blue-green cytoplasmic inclusions, pseudo-Pelger-like nuclei, fetal-like appearance	[8],[11-18],[20-24],[28],[29]
Lymphocyte	Activated/atypical lymphocyte, lymphoplasmacytic cells with eccentric nuclei, dark-blue basophilic cytoplasm and a distinct paranuclear hof, circulating plasma cells	[8],[11],[13],[16],[17],[20],[22],[31-34]
Monocyte	Pleomorphic and vacuolated monocytes, blue-green inclusions	[13],[14],[19],[20],[22],[26],[28]
Eosinophil	Eosinophilic malformations (trilobed or unsegmented nuclei, hypogranulated cytoplasm, multiple vacuoles)	[19],[27],[35]
RBDs	Anisocytosis, spherocytes, stomatocytes, knizocytes and polychromasia, with countless mushroom-shaped cells, circulating erythroblasts and red cell fragments, nucleated cells, some basophilic stippling	[12-15],[36],[38],[39]
Platelets	Large vacuolated platelets, platelet aggregates and giant platelets, varying sizes of platelets, pseudopod-like protrusions	[8],[16],[35],[44]

RBCs=Red blood cells

dysplastic neutrophils, left-shift myeloid series with immature promyelocytes and metamyelocytes, as well as atypical lymphocytes, lymphoplasmacytic cells, pleomorphic and vacuolated monocytes with blue-green inclusions, unsegmented nuclei, and hypogranulated cytoplasm of eosinophils. In addition, we have observed anisocytosis and spherocytes in RBCs, along with red cell fragments. Large vacuolated platelets and platelet aggregates have also been noted. It is important to recognize that although the changes in blood cells mentioned above are commonly found in COVID-19 patients, they are not exclusive to the disease. Many of these alterations, such as dysplastic neutrophils and left-shift myeloid series, can also be present in other viral or bacterial infections, as well as in cancer. Likewise, atypical lymphocytes and lymphoplasmacytic cells can be observed in a range of viral infections, including Epstein–Barr virus, cytomegalovirus, and hepatitis viruses. Furthermore, anisocytosis and spherocytes can be seen in other conditions, such as autoimmune hemolytic anemia. Thus, it is essential to evaluate these changes in the context of other clinical and laboratory findings rather than relying solely on peripheral blood cell morphology to diagnose COVID-19. Although these changes can provide vital insights into the severity and progression of the disease, they must be interpreted alongside other factors, such as patient symptoms, radiographic findings, and laboratory results, including PCR and serology testing. While the changes observed in the blood cells of COVID-19 patients may aid in diagnosing and managing the disease, they are not exclusive to COVID-19 and must be analyzed in the context of other clinical and laboratory findings.

The relationship between inflammatory markers, T-cell counts, morphological changes, and coronavirus disease 2019 severity and outcome

There is no association between markers of inflammation, such as ferritin, D-dimer, C-reactive protein, and lactate dehydrogenase, as well as the count of CD4 and CD8 T-cells, and abnormal morphological changes in peripheral blood film. However, these markers of inflammation, along with the count of CD4 and CD8 T-cells, are commonly used to assess disease severity and prognosis in COVID-19 patients [Table 2].

Conclusions

The examination of peripheral blood cell morphology is an important method for evaluating the severity and advancement of COVID-19. Patients with severe symptoms have been observed to exhibit nuclear dysmorphic and cytoplasmic changes in their neutrophils. In addition, activated/atypical lymphocytes and large vacuolated platelets have been linked to more severe cases of COVID-19. Fragmented neutrophils are highly sensitive morphological indicators of COVID-19, while circulating plasmacytic or plasma cells are highly specific. Severe COVID-19 patients in ICUs often have thrombocytopenia, and the existence of platelet aggregates and macrothrombocytes in their peripheral blood suggests increased platelet activity. Platelet aggregates may be used as a marker of worsening disease, but more research is needed to determine their role in COVID-19 pathogenesis and correlation with patients' outcomes. Several studies have emphasized the importance of conducting morphological studies on peripheral blood smears at both the baseline and follow-up stages. Most patients with moderate-to-severe symptoms show structural changes. Therefore, monitoring the shape of peripheral blood cells may help predict the severity of post-COVID syndrome. Performing a daily complete blood count on hospitalized patients with COVID-19 is essential to detect numerical and morphological abnormalities indicative of poor clinical outcomes and signs of disease progression.

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Table 2: Markers of inflammation and their contribution to the severity and outcome of coronavirus disease 2019

Inflammation marker	Association with COVID-19 severity/outcome	Reference(s)
Ferritin	Elevated ferritin levels have been associated with increased severity and mortality in COVID-19 patients. In addition, elevated ferritin levels have been linked to poorer outcomes in COVID-19 patients, such as longer hospital stays and higher mortality rates	[3],[48]
D-dimer	Elevated D-dimer levels have been associated with increased severity, higher rates of thrombosis, and mortality in COVID-19 patients	[49],[50]
CRP	Elevated CRP levels are associated with increased severity, higher rates of ICU admission, and mortality in COVID-19 patients	[50-52]
LDH	Elevated LDH levels are associated with increased severity and mortality in COVID-19 patients and are also linked to poorer outcomes, including higher mortality rates	[50-52]
CD4 T-cell	Reduced levels associated with severity of COVID-19 and poorer outcomes	[53 - 55]
CD8 T-cell	Reduced levels associated with severity of COVID-19 and poorer outcomes	[51], [53], [55], [56]

COVID-19=Coronavirus disease 2019, CRP=C-reactive protein, LDH=Lactate dehydrogenase, ICU=Intensive care unit

Conflicts of interest

There are no conflicts of interest.

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