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Convolutional Neural Network-Based Image Recognition Systems: Detecting the Peripheral Granular Lymphocytopenia and Dysmorphic Leukocytosis as Prognostic Markers of COVID-19

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Abstract

Developing prognostic markers can aid in clinical decision making. Peripheral Blood (PB) testing is a simple and basic test that can be performed at any facility. Changes in blood cell morphology as prognostic indicators of coronavirus infection (COVID-19) have been studied using an automated image recognition system based on Convolutional Neural Networks (CNNs). The incidence of anemia, lymphopenia, and leukocytosis was significantly higher in severe cases than in mild cases. Granulocyte counts were persistently decreased in the lethal cases but remained normal or higher in the mild cases. A transient increase in granulocytic lymphocytes was associated with survival in patients with severe infection, and neutrophilic dysplasia was observed in severe COVID-19 cases. Giant neutrophil number and toxic granulation tissue/Döhle bodies were increased in severe cases. Erythrocyte distribution was significantly larger in severe cases than in mild cases. Blood cell calculation using basic PB testing and the detection of morphological abnormalities utilizing CNN may be useful in predicting the prognosis of COVID-19.

Keywords: Prognostic markers; Acute respiratory syndrome; Lymphocytes; Blood cell; COVID-19

Description

Most patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infections (COVID-19) have mild symptoms, but some develop cytokine storms, leading to acute respiratory distress syndrome and multiple organ failure [1].

To correlate disease severity of COVID-19 with prognosis, various laboratory markers have been examined. For example, Procalcitonin (PCT) and interleukin-6 (IL-6) have been found to be associated with disease severity [2]. However, tests for these markers are expensive and not always available in routine clinical practice. Therefore, the feasibility and usefulness of tests for more accessible laboratory markers to determine severity has been investigated. Blood counts and biochemical test parameters can be quickly measured in basic clinical laboratories with relatively low costs. Among these parameters, the combination of Red Blood Cell Distribution Width (RDW), lymphocyte%, urea nitrogen, total protein and ferritin has been shown to be a useful combination marker for severity classification [3].

Furthermore, Peripheral Blood (PB) cell morphology findings by a Convolutional Neural Network (CNN)-based imaging system have shown that PB is useful as a prognostic marker for COVID-19 [4].

Findings in basic haematological tests

Characteristic findings in blood cell counts of COVID-19 cases include leukocytosis, lymphopenia, monocytopenia and thrombocytopenia [5]. Morphological examination has shown increased reactive lymphocytes, reactive T cells, Pelger-Hughes Anomaly (PHA), leukopenia and abnormal platelets in COVID-19 cases [6]. In addition, white blood cell count, neutrophil count, neutrophil lymphocyte ratio, immature granulocytes count, RDW and C-reactive protein levels were significantly higher in patients with severe COVID-19. In contrast, lymphocyte count, reactive lymphocyte count, haemoglobin and platelet count are known to be significantly lower in severe cases than in mild cases.

Since the analysis of blood cell morphology is subjective, the use of digital platforms equipped with automated image recognition systems using CNNs may be useful [4,7]. A previous study used a CNN-based analysis system and was able to show an increase in reactive lymphocytes in COVID-19 [7]. Since SARS-CoV-2 causes various abnormalities in blood cells of all lineages [6] a subsequent attempt was made to detect more detailed hematopoietic abnormalities in COVID-19 utilizing a digital CNN analysis system [4].

Morphological changes in white blood cells of COVID-19

In PB smears taken from COVID-19 cases, samples from both mild and severe cases show PHA, increased monocyte neutrophils, degranulation/overgranulation%, abnormal chromatin%, and other neutrophilic dysplasia. Several infectious diseases, including tuberculosis and viral infections such as human immunodeficiency virus, Epstein-Barr virus, and parvovirus, are known to stress the bone marrow, causing hematopoietic dysfunction and the appearance of PHA [8].

However, these dysplastic abnormalities were not significantly different between mild and severe cases of COVID-19. On the other hand, toxic changes, Döhle bodies, cytoplasmic vacuoles, and giant neutrophils % have been reported to be significantly higher in COVID-19 patients than in Healthy Control (HC) and were higher in the severe group than in the mild group [4,6,7]. In secondary bacterial and fungal infections, including sepsis, neutrophil abnormalities such as toxic granules and Dohle bodies appear [9]. These changes may indicate that severe SARS-CoV-2 infection triggers a systemic inflammatory response.

One of the haematological changes caused by SARS-CoV-2 infection is lymphocytopenia, and changes in lymphocyte subsets are associated with disease activity [10]. Specifically, in severe cases, the absolute number of reactive lymphocytes is known to be markedly reduced.[5] Lymphocyte morphology changes are also often observed in COVID-19, with mild COVID-19 cases tending to have a significantly higher percentage of granular lymphocytes compared to HC [4]. This is significant because granular lymphocytes are composed of natural killer cells and activated T cells, which are the major mediators of cytotoxicity [11,12].

It has been reported that CD8 killer T cells are decreased in severe cases of COVID-19 compared to mild cases [13]. Furthermore, a kinetics study showed that granulocyte count remains at very low levels during the clinical course in lethal cases, but transiently increases during the clinical course in recovered severe cases [4]. In addition, single-cell RNA sequencing studies have reported that active state T cells and cytotoxic NK cells are impaired in severe COVID-19 and the number of T cells in the active state is reduced [14]. In previous studies, CD8-killer T cells have been shown to play an important role in virus elimination following acute respiratory infection with Respiratory Syncytial Virus (RSV), Influenza A Virus (IAV) and human metapneumovirus [14,15]. These findings suggest that increased granular and reactive lymphocytes are associated with an effective immune response. Therefore these changes in PB smears may serve as promising markers of early-stage recovery from severe COVID-19

Conclusion

Previous studies have shown that SARS-CoV-2 infection induces multisystem changes in blood cell count and morphological abnormalities. These include abnormal neutrophil formation, such as PHA, monocytic neutrophils, degranulation/hyper granulation, and abnormal chromatin in all COVID-19 patients, regardless of severity. In addition, toxic changes, Döhle bodies, cytoplasmic vacuoles, and giant neutrophils have been reported in severe cases of COVID-19, as well as neutrophil changes due to a systemic inflammatory response. Regarding lymphocyte changes, an increase in granular lymphocytes was found in mild cases, and a persistent decrease in granular lymphocytes was found in lethal cases. PB cell morphology changes in COVID-19 are dynamically correlated with disease severity and may be related to bone marrow stress-induced hematopoietic and immune system destruction in severe infection. The detection of morphological abnormalities using CNNs may be useful for determining COVID-19 prognosis via PB smear tests.

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