Hematological Abnormalities in Patients With COVID-19: An Emerging Approach to Differentiate Between Severe COVID-19; Compared With Non-Severe Forms of the Disease

Mahdieh Mehrpouri

Department of Laboratory Sciences, School of Allied Medical Sciences, Alborz University of Medical Sciences, Karaj, Iran

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Abstract- The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a pandemic threat from December 2019. Coronavirus can cause varying degrees of illness that range from mild to severe or fatal disease. The exact mechanism on hematopoiesis induced by this coronavirus is not yet well understood, but scientific evidence indicates that COVID-19 can cause hematological changes in infected patients. The present study summarized pieces of literature regarding hematologic findings of COVID-19 and their correlation with disease severity. Finally, we offered some laboratory abnormalities which help to differentiate severe COVID-19 from non-severe forms of the disease. Among hematological parameters, decreased hemoglobin rather than anemia, leukocytosis, lymphopenia, neutrophilia, and thrombocytopenia have been observed in conducted studies in some patients with COVID-19. Furthermore, as the disease progresses to severe COVID-19, hemoglobin decline, leukocytosis, lymphopenia, neutrophilia, and thrombocytopenia continue to exacerbate. In addition, the neutrophil-to-lymphocyte ratio is also considered as an independent risk factor for severe infection in COVID-19 patients.

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Keywords: Coronavirus disease (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Hemoglobin; Lymphopenia; Neutrophilia; Thrombocytopenia

Introduction

In December 2019, the 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China, as an epidemic outbreak, but continued to rapidly evolve and convert to the pandemic that has prompted a lot of concerns (1,2). SARS-CoV-2 is a new human coronavirus belonging to the genus coronavirus, the family coronaviridae, and responsible for the coronavirus disease (COVID-19) (3). The incubation period of COVID-19 is on average 5-6 days; however, it can be up to 2 weeks or even longer (4,5). Coronavirus can cause varying degrees of illness from fever, cough, myalgia, or fatigue to systemic symptoms involving multiple systems, including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems (6-8). Nevertheless, the main target organ is lung tissue and respiratory complications, including severe acute respiratory syndrome and the Middle East respiratory syndrome, which are the leading cause of death in COVID-19, indicating a major challenge to clinicians in terms of disease management (9-12). However, many patients can be maintained using mechanical ventilators temporarily until their lungs recovery (13). Recent studies indicated that excess production of inflammatory cytokines in COVID-19 contributes to severe lung injury, acute respiratory distress syndrome (ARDS), and multiple organ failure (14). It seems that COVID-19 is not very different from SARS, another acute respiratory syndrome, regarding its clinical features; however, it has lower mortality rates than SARS and can spread faster than SARS in the community (3). Previous studies showed that

Corresponding Author: M. Mehrpouri
Department of Laboratory Sciences, School of Allied Medical Sciences, Alborz University of Medical Sciences, Karaj, Iran
Tel: +98 2634349800, Fax: +98 2634349800, E-mail address: mahdiyemehrpoori@gmail.com

hematological changes are a common finding among patients with SARS and remarkably comprise thrombocytopenia and lymphopenia (15-20). A compelling body of evidence indicates that COVID-19 also was prone to cause hematological changes in infected patients (21). However, the exact mechanism on hematopoiesis induced by this coronavirus is not yet well understood. In the present study, we summarized literatures and discussed challenges regarding to hematologic findings of COVID-19 and their correlation with disease severity and prognosis. Finally, we proposed several laboratory abnormalities which help to differentiate severe and fatal COVID-19 from non-severe forms of disease.

Hematological findings in COVID-19 patients and their correlation with prognosis

Anemia

Anemia of inflammation in hospitalized and chronically ill patients is the second most prevalent form of anemia, which is induced in response to immune cell activation and cytokines production (22). As far as COVID-19 infection is concerned, several studies stated that infected patients with COVID-19 show high levels of pro-inflammatory cytokines and chemokines (23,24). In Singapore, FAN *et al.*, found that patients with COVID-19 may have anemia of inflammation which require blood transfusion (25).

Moreover, in the study of Wenzhong *et al.*, bioinformatics analyses were used to evaluate the biological roles of specific proteins of this novel coronavirus. The results of this study showed that some viral proteins such as orf1ab, ORF3a, and ORF10 can attack the heme groups of hemoglobin beta chain, dissociating iron to form porphyrin which results in reduction in the oxygen-carrying capacity of hemoglobin (26). In the report of Lazarian *et al.*, they described 7 patients who developed the first episode of autoimmune hemolytic anemia (AIHA) during infection with COVID-19 after symptoms start in a timeframe compatible with the cytokine storm characterized by evidently increased levels of interleukins (27). AIHA is an acquired autoimmune disorder characterized with destruction of red blood cells by autoantibodies directed against red blood cell antigens resulting in reduced survival of erythrocyte (28). Association of viral infection with the development of autoimmune cytopenias mediated by autoantibodies has been reported in several studies (29,30), suggesting the possible role of COVID-19 in pathogenesis of AIHA. In a case report study conducted by Lopez et al, simultaneous presentation of COVID-19 disease and warm AIHA was reported in a 46-year-old female, suspecting that as her infection clears, the anemia will go away (31). Moreover, it has been claimed that SARS-CoV-2 infection acts as a potential trigger for AIHA, especially in patients who have immune dysregulation syndrome (32). Nevertheless, anemia is not a common laboratory finding in COVID-19 disease. However, a decreasing trend in hemoglobin level is observed. A meta-analysis with 1582 COVID-19 patients reported that patients in the severe group had significantly lower hemoglobin levels than those with non-severe ones (33). It seems that the reduction of hemoglobin should be more noticeable in intensive care unit (ICU) patients who require invasive ventilation compared with non-ICU patients. In the report of Fan *et al.*, although there was no difference in the admission hemoglobin between ICU patients and non-ICU patients (13.2 (12.5-14) g/dL vs. 14.2 (12.9-15.2) g/dL, P=0.07), hemoglobin of ICU patients decreased more significantly during the hospitalization (11.1 (10.2-11.9) g/dL vs. 13.6 (12.7-15.1) g/dL, P<0.001) (34). Consistently, Hung *et al*., found similar findings in comparison of admission hemoglobin between ICU patients and non-ICU patients (12.2 (11.1-12.8) g/dL vs. 13 (12-14) g/dL, P=0.2) (19). Despite the viral interference with erythropoiesis, which results in low hemoglobin levels, most COVID-19 patients did not require blood transfusions, probably due to the long life span of erythrocyte and the compensatory erythroid proliferation. Finally, the decline of hemoglobin level rather than anemia might be an indicator of COVID-19 progression.

Leukocytosis

Absolute leukocyte count and leukocyte differential count may have a fundamental value in screening, diagnosing, or staging of COVID-19 patients. A case report study conducted by Guoguang *et al*., evaluated blood parameters in a severe COVID-19 patient who was hospitalized for 26 days. Although the white blood cell (WBC) count on the first day of admission was normal, they showed dynamic changes in routine blood parameters such as WBC during hospitalization that might be useful in prognosis and evaluation of the treatment effect in COVID-19 patients (35). A study of 91 patients with COVID-19 demonstrated that although leukocytosis (>10×10^9/L) was noted on admission in 16.7% of severe COVID-19 disease compared to 9.8% of mild COVID-19 disease, most COVID-19 patients with severe (60%) and mild (57.4%) disease had normal leukocyte count (4-10×10^9/L) on admission (36). In another report, Fan *et al*., showed that most patients had

a normal leukocyte on admission with no statistically significant difference between two groups of ICU-patients and non-ICU patients (5.1 (3.5-8.2)×10^9/L vs. 4.7 (4.0-5.8)×10^9/L, *P*=0.87) (34). In contrast, Huang *et al.*, found that WBC on admission was higher in ICU patients than non-ICU patients (11.3 (5.8-12.1)×10^9/L vs. 5.7 (3.1-7.6)×10^9/L, *P*=0.011) (19). Of particular interest, a variety of studies have shown that patients with severe and fatal disease had significantly increased WBC count. A meta-analysis of the extant literature on 2635 patients noted that severe COVID-19 compared to non-severe COVID-19 had more significant increases in WBC count (weighted mean difference (WMD) (95% CI) 0.41 (0.16, 0.66)×10^9/L). Moreover, the same trend was also found in non-survivors compared to survivors, manifesting significant leukocytosis in non-survivors (WMD (95% CI) 4.15 (3.15, 5.15)×10^9/L) (33). Lippi *et al*., introduced leukocytosis as a hematological parameter to predict the severe COVID-19 disease (11.4% vs. 4.8%; OR, 2.54; 95% CI, 1.43-4.52) that can contribute to reflect the progress toward more disappointing clinical conditions (37). In COVID-19, leukocytosis appears to be characterized by neutrophilia, since lymphopenia developed simultaneously.

Lymphopenia

Lymphocytosis and lymphocytopenia (or lymphopenia) are conditions referred to an increase or decrease of lymphocytes in the bloodstream, respectively, that can be caused by various inherited and acquired diseases, including infectious diseases (38). A study in 99 patients with COVID-19 indicated that lymphocytes were below the normal range in 35 % cases, proposing that SARS-CoV-2 might mainly act on lymphocytes. Respiratory viruses are transmitted through the mucosa and infect other cells, persuade a cytokine storm which induce the alteration in peripheral leukocytes such as lymphocytes (39). These results further confirmed in another study conducted by Xu *et al*., which they found lymphopenia in 42% patients on admission (6). Subsequently, a study of 12 confirmed cases of SARS-CoV-2 infection from China measured blood count either on the date of hospital admission, or at the earliest time-point thereafter. They noted lymphopenia and decreased CD8 count in most cases (40). Furthermore, a case report study evaluated lymphocytes in a severe COVID-19 patient who was hospitalized for 26 days. On the first day of admission, lymphocytes decreased and reached a nadir on the 7th day of admission. In contrast to WBCs, neutrophils, monocytes and eosinophils which progressively increased and reached a peak on the 14th day, the number of lymphocytes did not reach the maximum value, but it showed an upward trend suggesting the gradual defense of leukocytes against viral infection (35). Similar results were found in the study from Zhang *et al*., the normal range of lymphocytes was 1.1-3.2×10^9/L, while the median lymphocyte was lower in COVID-19 patients (0.8 (0.6-1.1)×10^9/L) and lymphopenia was seen in 75.4% patients. They also found a positive correlation between eosinophil and lymphocyte numbers on the first day after hospital admission (r=0.321, *P*<0.001), indicating eosinophil count may be an important diagnostic clue that can be used as an indicator for COVID-19 infection in suspected cases (41). In general, it seems that lymphopenia may be considered as a common finding in COVID-19 patients, especially among hospitalized and severe COVID-19 patients, which predict unfavorable progression toward severe forms of COVID-19 and adverse outcomes (37,42-44). Several factors have been suggested that may be the underlying causes of lymphopenia in COVID-19 disease. Among them, it has been shown that the ACE2 receptor also is expressed on the surface of lymphocytes (45); therefore, SARS-CoV-2 can directly infect these cells and eventually causing their lysis. Moreover, cytokine storms in COVID-19 cases may promote apoptosis or necrosis of lymphocytes that lead to lymphocytes exhaustion (13). In general, multiple mechanisms may work together to induce lymphocytopenia that indicates coronavirus may consume immune cells and inhibit cell-mediated immune responses.

Numerous studies have been done to compare lymphocytes between different classes of disease. In this regard, a study of 29 patients with COVID-19 admitted to the isolation ward indicated that although the blood test of the patients showed decreased lymphocyte count (20 cases from 29), there was no statistically significant difference in lymphocyte count among three groups mild (15 cases), severe (9 cases) and critical (5 cases) (*P*>0.05) (46). Nevertheless, numerous studies have shown a significant difference in the lymphocyte count according to the disease severity. In this context, a study of 1099 patients showed that lymphocytopenia (<1.5×10^9/L) was present in 83.2% of the patients on admission, and patients with severe disease had more prominent lymphocytopenia than those with the non-severe disease (0.8 ×10^9/L vs. 1.0 ×10^9/L) (7). In another study, the surviving group exhibited a higher baseline value of lymphocyte count than the non-surviving group (1.1±0.5×10^9/L vs. 0.8±0.4×10^9/L, *P*<0.001). But, the non-survivors had a higher WBC count (7.6±3.3×10^9/L vs. 5.4±3.1×10^9/L, *P*<0.001) and neutrophil count

(6.3±3.3×10^9/L vs. 3.8±2.9×10^9/L, *P*<0.001) compared with the survivors, which may be related to inflammation and immune responses in the non-survivors (11). In the study of 107 patients with COVID-19, it has been indicated that lymphopenia (0.9 (0.7-1.2)×10^9/L) is among prominent features at admission, especially in the non-survivors compared to the survivors (0.8 (0.5-1.1)×10^9/L vs. 0.9 (0.7-1.3)×10^9/L). Further study for three weeks after illness onset showed, although mild cases had clinically resolved, lymphopenia was persistent in both the survivors and non-survivors of patients, suggesting that the lymphocytes count recovery is time-dependent (47). A recent meta-analysis study that extracted the data of 2556 patients, demonstrated that not only patients with severe and fatal disease had significantly decreased lymphocyte count compared to non-severe disease (WMD (95% CI) -0.28 (-0.32, -0.25)×10^9/L), but also non-survivors compared to survivors had a significant decrease in lymphocyte count (WMD (95% CI) -0.44 (-0.54, -0.35)×10^9/L) (33). Similar finding was obtained by Huang *et al*., where they showed 63% of patients (26/41) had lymphopenia on admission including 85 % of ICU-patients (11/13) and 54 % of non-ICU patients (15/28) (19). In the recent study, Fan et al showed that although the mean value of lymphocyte was normal in (1.2 (0.8-1.6)×10^9/L) in overall patients on admission, but there was statistically significant difference between two groups ICU-patients and non-ICU patients (0.5 (0.48-0.8)×10^9/L vs. 1.3 (0.9-1.7)×10^9/L, *P*=0.0002). Of particular interest, during hospitalization, the lymphocyte of the ICU patients decreased more significantly compared to non-ICU patients during the hospitalization (0.4 (0.3-0.5)×10^9/L vs. 1.2 (0.8-1.6)×10^9/L, *P*<0.001) (34). Contrary to many current studies, in a study on 91 patients diagnosed with COVID-19, 30 cases (33.0%) were severe and 61 cases (67.0%) were mild. The results showed 51.6% of patients had lymphopenia on admission, which unexpectedly was more prominent in mild cases (59 % of mild cases vs. 36.7% of severe cases) (36). The exact reasons for these inconsistencies are not clear, however, several factors may be involved including age of patients, ethnicity and time of testing. Finally, according to the conducted studies, lymphopenia can be used as an effective indicator in the severity of illness in COVID-19 patients (48).

Neutrophilia

Reports from experts in this field propose that ICU patients were more likely to have neutrophilia, suggesting it as an indicator of advanced disease. A study of 138 patients with COVID-19, including ICU patients (n=36) and non-ICU patients (n=102), demonstrated that patients admitted to the ICU have higher WBC and neutrophil counts compared to those not admitted to the ICU (4.6 (2.6-7.9)×10^9/L vs. 2.7 (1.9-3.9)×10^9/L, *P<.001*) (13). Similarly, in the study of Hung et al., they indicated that patients who had been admitted to the ICU had higher neutrophil count (10.6 (5.0-11.8)×10^9/L vs. 4.4 (2.0-6.1)×10^9/L, *P*=0.00069) compared with non-ICU patients (19). Moreover, Zhao et al. showed that the neutrophil count on admission in the non-surviving group was significantly higher than those of the surviving group (6.3±3.3×10^9/L vs. 3.8±2.9×10^9/L, *P*<0.001), which may be related to inflammatory and immune responses in non-survivors (11). Furthermore, a study of 99 confirmed cases of SARS-CoV-2 infection showed that 38% of patients had neutrophils above the normal range (5.0 (3.3-8.1)×10^9/L vs. 1.8-6.3×10^9/L) (39).

Another study in 383 COVID-19 patients showed that thrombocytopenic patients had lower neutrophil count compared with non-thrombocytopenic patients (2.8 (1.5-3.8)×10^9/L vs. 3.3 (2.2-4.7)×10^9/L, *P*=0.005) (48). Although, the study of Zhao *et al*., in 91 patients showed that there was no significant difference between mild and severe cases with respect to neutrophil count (36). A meta-analysis of the extant literature on 1506 patients indicated that severe cases compared to non-severe cases of COVID-19 had more significant increases in neutrophil count (WMD (95% CI) 1.7 (1.57, 1.85)×10^9/L) (33). Similar results were found in the study of Wang *et al*., where they observed that survivors compared with non-survivors had higher neutrophil counts on admission (5.4 (3.2-8.5)×10^9/L vs. 2.8 (2-3.9)×10^9/L, *P*<0.001) (47). The cytokine storm, hyperinflammatory state, and super bacterial infection caused by COVID-19 may be related to neutrophilia. Neutrophilia predicts poor outcomes in COVID-19 patients, and the neutrophil-to-lymphocyte ratio (NLR) is regarded as an independent risk factor for severe illness in these patients (13,37,49). The ability of neutrophils to form neutrophil extracellular traps (NETs) may contribute to organ failure and mortality in COVID-19 (45).

Thrombocytopenia

Alterations in platelet count are usual in COVID-19 patients and reveal the pathophysiologic changes in COVID-19 patients (11). Moreover, a low platelet count associates with higher risk and disease severity (50). In the study of Liu et al. on 383 patients with COVID-19, the results showed that most patients had normal platelets, and a few had thrombocytopenia (48). Moreover, in the

study of Chen *et al*., on 99 patients, platelet counts were below the normal range in 12% patients and above the normal range in 4% patients (39). Similar findings were obtained in the study of Hung *et al*., on 41 patients in Wuhan, where indicated that 5% of patients had thrombocytopenia (Platelets count $<100\times10^9$/L) on admission, although, there was no significant differences in comparing ICU patients and non ICU patients in platelet count (196.0 (165.0-263.0)$\times10^9$/L vs. 149.0 (131.0-263.0)$\times10^9$/L, *P*=0.45) (19). In the study of 532, the results showed that although there was no significant difference between survivors and non-survivors on admission (176.0×10^9/L vs. 171.7×10^9/L, *P*=0.826 in male and 194.7×10^9/L vs. 180.3×10^9/L, *P*=0.466 in Female), nevertheless, the platelet count of non-survivors decreased significantly compared with survivors on 14-15th day especially in male patients (114.3×10^9/L vs. 239.9×10^9/L, *P*=<0.001 in male and 151.1×10^9/L vs. 250.7×10^9/L, *P*=0.001 in female) (11). Results from a meta-analysis of twelve studies showed that not only severe cases had decreased number of platelets compared with non-severe cases (WMD (95% CI) -23.36 (-30.82, -15.89)$\times10^9$/L), but also non-survivors compared to survivors had more significant decrease in platelet count (WMD (95% CI) -48.3 (-57.67, -38.93)$\times10^9$/L), suggesting that platelet count can be used as potential predictors of severe and fatal disease (33). Consistent with these studies, another meta-analysis of 1779 COVID-19 patients revealed that platelet count was significantly lower in patients with more severe COVID-19 (WMD (95% CI) -31 (-35, -29) $\times10^9$/L) (51).

Platelet changes likely contribute to their recruitment as an anti-inflammatory factor (35). Since platelets production are also conducted in the lungs, thrombocytopenia in COVID-19 patients may be due to increased destruction or reduced production of platelets in damaged lungs (52,53). Furthermore, platelets may be consumed in disseminated intravascular coagulation in these patients (37).

Coronavirus family have led to few epidemics and a new pandemic in last 2 decades with various clinical manifestations from self-limiting illness to fatal disease. Hematological abnormalities may be observed in patients with COVID-19, which is caused by SARS-CoV-2. Among them, decreased hemoglobin, leukocytosis, lymphopenia, neutrophilia, and thrombocytopenia have been seen in many studies. As the disease progresses to severe and fatal COVID-19, hemoglobin decline, leukocytosis, lymphopenia, neutrophilia, and thrombocytopenia continue to exacerbate. Moreover, the neutrophil-to-lymphocyte ratio is considered as an independent risk factor for severe infection in these patients. Finally, these findings should continually re-evaluate in the future as more information becomes available.

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