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Hematologic Parameters of COVID – 19: A Review on Alteration of Hematologic Laboratory Findings

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Abstract

Corona virus 2019 (COVID –19) is a public health emergency and according to the recent statistic of World Health Organization (WHO), this novel virus has infected all continents. During this outbreak, there is an urgent need for documentation of laboratory predictors to discriminate between mild and severe forms of this virus. In this pandemic, prompt identification of clinical and laboratory prognostic factors of progression towards critical and lethal forms of this disease is mandatory. During this new infection, lymphopenia, thrombocytopenia, sometimes neutrophilia, elevation of D-dimer, prolongation of prothrombin time (PT), and Partial Thromboplastin Time (PTT), and also increased level of fibrin degradation products (FDP) could occur. Moreover, elevation of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, ferritin, Lactate dehydrogenase (LDH), and interleukin -6 (IL- 6) are other laboratory features. These parameters will enable risk stratification and favorable allocation of limited and technical resources particularly in under developed countries. In this review article, alteration of hematologic laboratory findings has been discussed.

Key Words: Covid-19, Coagulation, Hematology, SARS-CoV-2, Thrombocytopenia.

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1- INTRODUCTION

The 2019 novel coronavirus (2019–nCOV) or the severe acute respiratory syndrome corona virus 2 (SARS – COV – 2) as it is now called, is a public health emergency. The first origin of this novel virus was from Wuhan city of Hubei Province of China and then it rapidly spread from its origin to other parts of the world (1). Corona viruses have a positive sense single stranded RNA genome and sequence analysis of the genome of COVID -19 has an obvious similarity to SARS – like corona viruses that normally infect bats (2). Up to now, there is no specific vaccine or antiviral agent for this problematic virus. While many infected individuals have mild to moderate symptoms, a number of patients develop severe and profound inflammatory response leading to acute lung injury, and hypoxemic respiratory failure. Acute respiratory distress syndrome (ARDS) is the most common cause of death in patients with COVID -19 (3).

During this outbreak, prompt identification of clinical and laboratory prognostic factors of progression towards critical and lethal forms of this disease is mandatory. Furthermore, these laboratory parameters will enable risk stratification and differentiation between severe and non-severe cases. Also, discriminating between high risk and low risk infected individuals allows us to optimize the allocation of limited resources in this situation. Obviously a clear pattern of inflammatory hematologic and immune parameters abnormalities could be found between patients with or without severe or critical disease (4). Among these markers, hematologic profiles such as absolute lymphocyte count and platelet count are simple and available parameters which are independently correlated with disease severity and risk of mortality in patients who were admitted in intensive care units (ICU) (5). The results of multiple studies about COVID -19 have documented that the hematology laboratory acts as an important component in the triage and management of infected individuals (6). Although the alteration of lymphocytes, platelets, neutrophils or acute phase reactants are not specific or diagnostic for this novel virus (like RT – PCR), their value as prognostic indicators has been established (6). In this review article, the major hematologic features of this novel virus have been discussed.

2- MATERIALS AND METHODS

In this review, an electronic search was performed in databases of Scopus, EMBASE, Cochrane, Web of Science and Medline (via PubMed) within English literature (up to July 24, 2020). The single and combination keywords of: "2019 novel coronavirus" or "2019-nCoV" or "COVID-19" or "Severe acute respiratory syndrome coronavirus 2" or "SARS-CoV-2" or ("Wuhan" and "Coronavirus") or "Coronavirus" and "Laboratory" or "Hematology" were used. The references of all included articles were searched to identify additional studies.

The title, abstract and full text of all documents identified using these search criteria were screened by a pediatric hematologist and oncologist and those describing significant laboratory hematology abnormalities in patients with COVID-19 infection were finally selected. Overall, 197 articles could be originally identified using search criteria, 174 of which were excluded after title, abstract or full text reading, because they did not report specific data on laboratory test results.

3- RESULTS

A total number of 23 studies were finally selected. The results of these studies have been classified in 3 groups: alterations of blood cells in CBC; coagulation abnormalities; and changes of

acute phase reactants or markers of inflammations.

3-1. Hematologic parameters

3-1-1. Lymphopenia

Lymphopenia is a common finding in patients with COVID -19 infection and is defined as an absolute lymphocyte count < 1.0×10^9 / L. This finding represents a defective immune response to the virus (6). Lippi et al. in a recent meta- analysis have shown that lymphopenia was seen in 35-75% of patients with COVID – 19. Furthermore, this finding was more common in patients who died of disease (7). Fan et al. in a study on 67 patients with SARS-COV- 2 infection in Singapore reported that a lymphocyte count below 0.6×10^9 / L is a valuable predictor for admission in ICU. In this study, 28% of all of patients with COVID -19 had lymphopenia (8). This number is significantly lower than the number of patients in other studies. Huang et al. in a study in Wuhan, China reported 63% of patients had lymphopenia and Xu et al. demonstrated that 42% of patients outside of Wuhan presented with lymphopenia (9, 10). However, there appears to be some geographic differences in the percentage of COVID-19 patients with lymphopenia. The exact etiology of these geographic variabilities in various reports from different parts of the world is not clear.

Regarding viral genomic mutations, it is possible that the immunologic reaction to the virus may alter as the pandemic expands into different parts of the world. Another reason for these discrepancies is that testing of patients is not identical worldwide and depending on time of presentation, the severity of lymphopenia may vary (6). Henry et al. in a meta-analysis on infants and children have shown that lymphopenia is much less common. These authors showed that only 3% of infants presented with lymphopenia. This is in contrast to SARS and MERS infection, because in both of these infections, lymphopenia is a common feature. In very young children, lymphopenia may not develop due to reactive immaturity of their immune system (11). Four potential mechanisms are responsible for lymphopenia in COVID – 19. At first, this virus may directly invade lymphocytes leading to lymphocyte death. Lymphocytes express angiotensin converting enzyme 2 (ACE 2) receptor which is specific for corona virus and is a direct target for this agent. Secondly, SARS-COV- 2 infection could directly destroy lymphatic organs, such as thymus and spleen. The third mechanism is the many inflammatory cytokines that are released during the course of COVID -19 infection may result in lymphocyte apoptosis. These cytokines including tumor necrosis factor α (TNF – α) and interleukin – 6 (IL – 6) may lead to lymphocyte deficiency.

Fourthly, coexisting lactic acidosis could inhibit lymphocytes. Hyperlactic acidemia, which is a complication of severe type of COVID -19 might suppress lymphocyte proliferation (12, 13). Wang et al. in a study on 60 hospitalized COVID-19 patients (before and after treatment) have measured peripheral lymphocyte subset by flow cytometry. Total lymphocytes, $CD4^+$, and $CD8^+$ T cells, B cells and natural killer (NK) cells decreased in COVID -19 cases and patients with severe type of infection had a lower level in comparison to mild cases. After treatment, 37 patients (67%) showed clinical response and $CD8^+$ T cells and B cells have been increased. In multivariate analysis, post treatment decrease in $CD8^+$ T cells and B cells and increase in $CD4^+$ / $CD8^+$ ratio was considered as independent poor prognostic factors. These authors have demonstrated that $CD4^+$ / $CD8^+$ ratio has a positive correlation with ESR, CRP and IL-6, while $CD8^+$ T cells have a negative correlation with these inflammatory markers. Also,

NK cells have a negative correlation with IL-6. Wang et al. have concluded that $CD8^+$ T cells have more profound alterations comparing with other lymphocyte subsets after COVID-19 infection (14). Fan et al. showed that these patients with COVID -19 who were admitted in ICU, have significantly lower $CD45^+$, $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16/56^+$ counts (8). Furthermore, during hospitalization, non-survivors showed a more pronounced lymphopenia compared with patients who survived (15). Also, in patients with severe COVID -19 and fatal outcome, lymphocyte /white blood cell ratio is much lower in comparison with milder forms both in admission and during hospitalization (16, 17). Therefore, serial measurement of lymphocyte count has a prognostic value in prediction of patient program (13).

3-1-2. Neutrophils

In patients with COVID–19, neutrophilia indicates cytokine storm and hyper inflammatory state. In these patients, during hospitalization a number of morphological variations both in cytoplasm and nucleus of granulocytes have been shown. Hyper segmented nuclei and apoptosis have been demonstrated in circulating polymorph- nuclear cells. These morphological abnormalities may be seen before the appearance of reactive lymphocytes. Furthermore, neutrophilia could be representative of a secondary bacterial infection (6). Also, the incidence of neutrophilia in ICU patients is higher in comparison with non-ICU group (8). Qin et al. have shown an increase in neutrophil to lymphocyte ratio in patients with severe COVID -19 infection (16).

3-1-3. Monocytes

In patients with severe SARS-COV- 2 infection, absolute monocyte count (AMC) decreases. Fan et al. have shown a significant decrease in AMC in ICU patients compared to non-ICU group (8). Henry et al. in a meta-analysis on 3,377 patients demonstrated reduction of monocytes in COVID -19 (18). It has also been shown that monocyte distribution width (MDW) increases in patients with COVID -19 particularly in severe types. However, the presence of reactive lymphocytes in SARS-COV- 2 infection may lead to falsely elevated MDW (6). Moreover, in peripheral blood of COVID -19 patients who were admitted in ICU, a prominent expansion of $CD14^+$ $CD16^+$ monocyte producing IL-6 has been observed (19).

3-1-4. Eosinophils

In early stages of COVID -19 infection, eosinophil count decreases. The mechanism of eosinopenia may be related to glucocorticoid exposure. Due to stress response in these patients, glucocorticoid secretion could result in inhibition of eosinophil release in the bone marrow. With improvement in clinical and radiological features, the eosinophils' count increases increase. Also, high eosinophil count in mild cases was earlier than that of severe cases. In other words, increased eosinophils could be an indicator of improvement in COVID -19 (20). Zhang et al. in a study on 140 hospitalized COVID -19 patients in China showed eosinopenia in 52.9% of cases. Also, these authors reported a positive correlation between eosinophil and lymphocyte counts. In patients with typical symptoms and radiological features with and without lymphopenia, eosinopenia may be a helpful diagnostic marker (21).

3-1-5. Thrombocytopenia

Thrombocytopenia is a significant finding in patients with severe type of COVID -19 (6). Lippi et al. have reported thrombocytopenia in 57.7% of severe COVID -19 infection, while 31.6% of patients with milder symptoms had thrombocytopenia (22). In another study, Guan et al. indicated that 36.2 % of

patients had thrombocytopenia (23). Besides, there is an association between thrombocytopenia and hospital mortality in COVID -19 (24). Platelet count is a readily available biomarker which has a significant association with disease severity in COVID -19 (5). The mechanism of thrombocytopenia in COVID-19 is multifactorial. Lung may be a site of platelet release from mature megakaryocytes. The lung megakaryocytes in response to the liver thrombopoietin could produce many platelets which contribute in the host defense against virus, hence platelets are one of the first lines of defense. COVID -19 could entrap megakaryocytes and therefore inhibit the release of platelets (25). Also, SARS-COV- 2 virus directly infects bone marrow resulting in damage to megakaryocytes and hence, thrombocytopenia. In addition, corona viruses may trigger an auto immune response against blood cells (5). Another probable mechanism for thrombocytopenia is consumption of platelets in pulmonary thrombi (25).

A bronchoalveolar hemostatic system exists which could inhibit invasion of pathogen into the circulation. When various parameters could not suppress the infection, pulmonary micro thrombi occur, therefore thrombus formation is an anti-infective mechanism. Furthermore, serial platelet counts monitoring in patients with COVID-19 has a significant role in prediction of patient's outcome. In infected individuals with SARS-COV- 2 who had nadir platelet count, the mortality decreased with increasing the number of platelets and indicates that thrombotic process has been diminished and platelets are no longer consumed in the clot. In low income countries, where access to laboratory tests is limited, clinicians could benefit from serial monitoring of platelets (25). Another prognostic factor which could predict prolonged hospitalization is platelet to lymphocyte ratio. A high platelet to lymphocyte ratio represents a cytokine storm and enhanced platelet activation (13).

3-2. Coagulation parameters

Many patients with severe COVID -19 infection present with coagulation abnormalities such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (26). Moreover, coagulopathy in COVID -19 infection has been associated with increased mortality rate (27). The most typical feature in SARS-COV- 2 infection and coagulopathy is increased level of D-dimer (26). Guan et al. in a study from China showed that in 46% of patients, the level of D-dimer increases (>0.5 mg/L) (23). Huang et al. have demonstrated that COVID -19 patients who were admitted in ICU wards, have a higher level of D-dimer in comparison with patients who have not received ICU care (9). In another study it has been reported that D-dimer on admission of more than 1mg/L has been associated with an 18-fold higher increased risk of death (28). Another laboratory finding in patients with severe COVID -19 infection is prolongation of prothrombin time (6, 26).

Other coagulation abnormalities may include prolongation of activated partial thromboplastin time (PTT), and elevation of fibrin degradation product (FDP) (27). In a study on 183 patients with severe novel corona virus pneumonia from China, authors found that non-survivors showed significant elevation of D-dimer, FDP, PT and PTT compared with survivors. In this study, overall mortality rate was 11.5% and 71.4% of non-survivors and 0.6% of survivors have the criteria of DIC (27). Furthermore, in patients with COVID– 19, a mild elevation of fibrinogen may be observed probably as an acute phase reactant. Plasma concentration of anti-thrombin is lower in COVID-19 non-survivors compared with survivors, however, it rarely drops below 80% of

normal level (26). Moreover, in critically ill patients with COVID–19, antiphospholipid antibodies and also increased arterial and venous thrombotic events such as cerebral infarction have been shown (29). Another interesting finding is that the pattern of DIC in COVID-19 is completely different from DIC due to sepsis. In sepsis, thrombocytopenia is often more severe and the level of D-dimer concentration is much higher in COVID-19 compared with sepsis (27, 30). However, post- mortem findings in SARS-COV- 2 infection show microvascular platelet rich thrombotic deposition in small vessels of lungs or other tissues. It seems that the coagulopathy during COVID-19 infection is a combination of low grade DIC and localized pulmonary thrombotic microangiopathy (26).

3-3. Acute phase reactants

3-3-1. C – reactive protein (CRP)

CRP is an acute phase reactant which is produced in the liver. This marker in severe types of COVID -19 increase in 75-93% of patients. Also, elevation of ESR has been reported up to 85% of cases (7).

3-3-2. Procalcitonin

Procalcitonin is a pro hormone which plays an important role in calcium homeostasis. Elevation of this marker may be seen in many inflammatory conditions and sepsis. In initial evaluations, many COVID -19 patients have normal procalcitonin levels, but after some time, particularly in patients who were admitted in ICU, a significant elevation of procalcitonin occurs. Serial monitoring of procalcitonin has been recommended in ICU patients to evaluate whether patients are developing worsening infection (6). Lippi and Plebani in a meta-analysis have shown that elevation of procalcitonin concentration has been associated with a 5-fold higher risk of severe COVID-19 infection. It seems although procalcitonin values are not modified in cases with viral infection, serial assessment of this marker may be of prognostic value in distinguishing patients with or without severe COVID -19 infection (31).

3-3-3. LDH

LDH is an enzyme that catalyzes the production of pyruvate to lactate. This enzyme is expressed in many human cells such as heart, kidney, muscle, lung, bone marrow and liver cells (6). Fan et al. in a study from Singapore demonstrated that LDH could serve as a parameter for discrimination between ICU and non-ICU patients and represents a worse outcome (8).

3-3-4. Serum Ferritin

Serum Ferritin is another acute phase reactant that could be associated with acute respiratory distress syndrome (ARDS) development in COVID -19 (32). Zhou in a retrospective study from Wuhan in China on 191 patients with COVID -19 had shown that serum ferritin has a significant elevation in non-survivor patients with COVID -19 in comparison with survivor patients (28). This marker has a prognostic value in COVID -19 patients during the course of hospitalization (4).

3-3-5. Interleukin – 6

In patients with profound elevation of inflammatory cytokines such as IL-6, a cytokine storm occurs which may lead to acute lung injury and multi organ failure. Also, a significantly greater increase was observed for IL-6 in non-survivors compared with survivors in COVID -19 infection. In hospitalized COVID-19 infected cases with respiratory distress, IL-6 could be considered a parameter for progression to critical disease (4). Liu et al. in a study on 140 patients with COVID-19 showed that IL-6 > 32.1 Pg. / ml or CRP > 41.8 mg / L has been correlated with severe complications (33). Moreover,

elevation of interleukin – 10 (IL-10) has been demonstrated in severe types of COVID -19 infection (4). Both IL-6 and IL-10 could predict disease severity in COVID-19 (34).

4- CONCLUSION

The novel coronavirus disease 2019 continues to progress toward a global pandemic. Therefore, assessment of the discriminative potency of hematologic marker in patients with and without the critical forms of COVID -19 is necessary. In hospitalized COVID -19 patients particularly with respiratory distress, close monitoring of WBC count, lymphocyte count, platelet count, serum ferritin and other markers of systemic inflammation is recommended.

5- ABBREVIATIONS

COVID–19: Coronavirus disease 2019.
WHO: World Health Organization.
PT: Prothrombin time.
PTT: Partial thromboplastin time.
FDP: Fibrin degradation products.
ESR: Erythrocyte sedimentation rate.
CRP: C-reactive protein.
LDH: Lactate dehydrogenase.
IL- 6: Interleukin -6.
SARS-CoV-2: Severe acute respiratory syndrome corona virus 2.
ARDS: Acute respiratory distress syndrome.
ICU: Intensive care units.
RT – PCR: Reverse transcription polymerase chain reaction.
CBC: Complete blood count.
SARS: Severe acute respiratory syndrome.
MERS: Middle East respiratory syndrome.
ACE 2: Angiotensin converting enzyme 2.
TNF – α: Tumor necrosis factor α.
CD: Cluster of differentiation.
NK: natural killer.
AMC: Absolute monocyte count.
MDW: Monocyte distribution width.
DIC: Disseminated intravascular coagulation.

6- CONFLICT OF INTEREST: None.

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