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Hematological Alterations Associated with COVID-19 Severe

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ABSTRACT

Since the onset of the COVID-19 pandemic in 2020, several studies have been relating the severity of the disease with hematological and coagulation changes besides a strong immune response. Understanding what these changes are, in addition to seeking predictive biomarkers of mortality, has become an essential task to help control and reduce the death rate during hospitalization of COVID-19 patients with a severe clinical conditions. The objective of this study was to evaluate the hematological alterations according to the clinical outcomes of COVID-19. Hematological alterations such as lymphopenia, leukocytosis, neutrophilia, and decrease in hemoglobin and red blood cells, in addition to a state of hypercoagulability and cytokine storm, have become the main alterations present in hospitalized patients with COVID-19. The initial identification of these abnormalities is useful for the early prognosis of individuals who may die during hospitalization and thus allow these patients to receive targeted support to improve their clinical condition.

Keywords: COVID-19 • Hematological • Abnormalities • Lymphopenia • Neutrophilia

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INTRODUCTION

The disease promoted by the novel coronavirus (Coronavirus Disease 2019), known as COVID-19, is transmitted by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was first identified in Hubei Province, Wuhan, China [1]. SARS-CoV-2 is a highly contagious virus that has spread over the globe in a brief period of time, and on March 12, 2020, the World Health Organization (WHO) announced COVID-19 a pandemic that has created numerous challenges to health systems in many countries [2].

To date, COVID-19 has harmed more than 400 million people throughout the world, taking more than 5 million deaths, and can present with different clinical pictures with systemic manifestations and different degrees of severity [3]. Furthermore, studies showed that in addition to the increased inflammatory response, declining age and the existence of comorbidities are conditions considered risk factors for the severity of COVID-19 [4].

Owing to the fact that COVID-19 is a new disease, there is a reasonable indefiniteness regarding the clinical and laboratory data and how these parameters are correlated to the severity [5]. In addition, SARS-CoV-2 infection may also be associated with a state of hypercoagulation with changes in several parameters involved in the coagulation cascade [6].

Furthermore, the excessive production of acute phase proteins and pro-inflammatory cytokines are intrinsically related to the patient's clinical condition, and may also act as predictors of disease severity as a result of the powerful association with multiorgan failure [7].

Hematological Alterations in COVID-19

Early hematological abnormalities in COVID-19 patients have also been associated with an elevated risk of mortality [8,9]. As for the hematological changes that may reflect the high severity, studies have shown that platelet counts, leukocytes, lymphocytes, hemoglobin, acute phase proteins such as ferritin and C-reactive protein, in addition to irregularities in the elements of coagulation cascade and fibrin degradation products such as D-dimer, were found in patients with severe COVID-19, as well as being associated with disease progression [10,11].

Previous studies have shown that SARS-CoV-2 infection is associated with an elevated incidence of thrombotic complications [12,13] and presented evidence that the virus could infect endothelial cells and lead to microcirculation changes, inflammatory cell accumulation and endothelial inflammation in patients with COVID-19 [14-16].

In this context, the American Society of Hematology indicates that COVID-19 is correlated with a clinical state of hypercoagulation with high concentrations of changes related to the coagulation cascade, including parameters such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), in addition to Fibrin Degradation Products (FDPs) such as D-dimer [17].

There are already consistent data in the literature that lymphopenia and neutrophilia are hematological alterations of severe COVID-19, in addition to being associated with a worse prognosis of the disease and a higher risk of death [18-20]. A recent retrospective study with more than 4,000 COVID-19 patients showed that non-survivor patients had a significant increase in total leukocyte and neutrophil counts, besides a decrease in lymphocytes and eosinophils [21].

Considering that neutrophils are quickly recruited to the spot of infection from the blood flow at the beginning of the viral infection, they are stimulated to differentiate and move out of the bone marrow. Earlier studies have shown that respiratory viral infections originating from MERS, respiratory syncytial virus, and influenza lead to massive amounts of neutrophils infiltrating the lungs of patients [22-24], and a study on the influenza virus showed that the intensity of neutrophil infiltration is associated to the type of viral strain, viral load and severeness of the disease [25].

It is common in viral infections for neutrophils to release chemokines and inflammatory cytokines such as CXCL-8, IL-6, and TNF-α to engage and activate more neutrophils and restrict the viral replication and limit the disease to advance [26]. Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), when identified by their respective receptors, are responsible for triggering the production of pro-inflammatory cytokines and chemokines responsible for neutrophil recruitment, such as CCL-2 and CXCL-8 [27,28].

In addition, the increase in neutrophils in the blood of hospitalized patients may be related to the thrombopathy associated with COVID-19, due to the formation of Neutrophil Extracellular Traps (NETs) that are released by activated neutrophils, stimulating the aggregation of platelets and triggering the coagulation cascade [29,30]. Moreover to the increase in neutrophils, one study demonstrated that the spike protein of SARS-CoV-2 can stimulate the release of NETs [31] and the intravascular formation of NETs with the aggregation of platelet that causes damage in some organs such as the heart, kidney, and lung due to the rapid occlusion of vessels [32,33].

A few mechanisms have already been proposed to clarify lymphopenia in patients with COVID-19. Mechanisms induced by SARS-CoV-2 include apoptosis, pyroptosis, bone marrow compromise, and thymus suppression, whereas mechanisms mediated by the immune response include the cytokine storm induced by the lymphocyte apoptosis, autophagy-mediated cell death, dependent cytotoxic T lymphocytes, autoantibodies or dendritic cells, in addition to metabolic and biochemical alterations that have an effect on the production and survival of lymphocytes [34,35].

Cytokine storm is likely a key factor behind the lymphopenia seen in COVID-19, and the concentration of cytokines such as IL-6 and TNF-α have been correlated with a decrease in circulating lymphocytes in the blood [36,37].

Elevated serum ferritin concentration is known as hyperferritinemia and is considered when above 400 ng/mL [38], with a minimum limit of 500 ng/mL for the diagnosis of macrophage activation syndrome [39]. The increase in ferritin associated with the reduction of cytotoxic lymphocytes, besides abnormal liver function tests and coagulopathy, allowed the scientific literature to agree that COVID-19 perhaps is the newest member in the hyperferritinemic syndromes that cause severe inflammation and may lead to multiple organ failure [40,41].

Some studies showed that during hospitalization of COVID-19 patients, hematological changes such as decreased hemoglobin, red blood cells, and monocyte counts were present [42-44], in addition to leukocytosis in patients who required Intensive Care Unit (ICU) admission [20].

The inflammation caused by SARS-CoV-2 infection can lead to an oscillation of iron homeostasis and decreased intestinal iron input, evolving to a lower suitability to produce erythrocytes and hemoglobin [45,46], which could

explain the decrease in the concentration of hemoglobin and red blood cells during the hospitalization period of COVID-19 patients.

Some studies have reported that there is a substantial decrease in hemoglobin in COVID-19 patients with a severe condition, compared to patients with a moderate clinical condition [46,47], as well as a reduction in patients who needed orotracheal intubation when compared to those who did not [48]. One recent study showed that not only is there a drop in hemoglobin in the peripheral blood, but this reduction is associated with an increased risk of death during hospitalization of patients with COVID-19 [49].

Scientific literature has shown that COVID-19 is a hematological and respiratory disease, however, some studies have shown that it may also be a vascular disease since it results in a permeable vascular barrier and is responsible for increasing elements of the coagulation cascade and releasing cytokines, establishing a process of inflammation [50-52]. This persistent endothelial activation may reflect in the rupture of vascular integrity and the activation of the coagulation cascade [53].

A meta-analysis study found that low platelet counts are related to a three-fold enlargement in the possibility of evolving into a severe clinical condition in COVID-19 [54]. Other studies have shown that SARS-CoV-2 infection is frequently linked with the activation of platelets and coagulopathy, and usually occurs at the beginning of the infection [55,56]. Furthermore, it has already been revealed that COVID-19 induces the immunothrombosis, a process in which the interplay between monocytes, neutrophils, platelets, and the coagulation cascade triggers the formation of intravascular clots in different vessels [57]. Another study showed that this mechanism of immunothrombosis is the key point between thrombotic events and multiple organ collapse [32].

In this sense, a significant imbalance in hematological and coagulation parameters, including acute phase proteins and inflammatory cytokines indicates a worse prognosis in the SARS-CoV-2 infection, culminating in a systemic inflammatory response with hematological changes such as lymphopenia, leukocytosis, neutrophilia, represented by Figure 1 summarizing the main hematological abnormalities in COVID-19: The infection with SARS-CoV-2 causes different hematological changes in individuals, especially in those with a severe clinical condition. Changes such as lymphopenia, neutrophilia, leukocytosis, and thrombocytopenia are often found in non-survivor patients, in addition to cytokine storm, higher concentrations of ferritin, C-reactive protein, and platelet consumption.

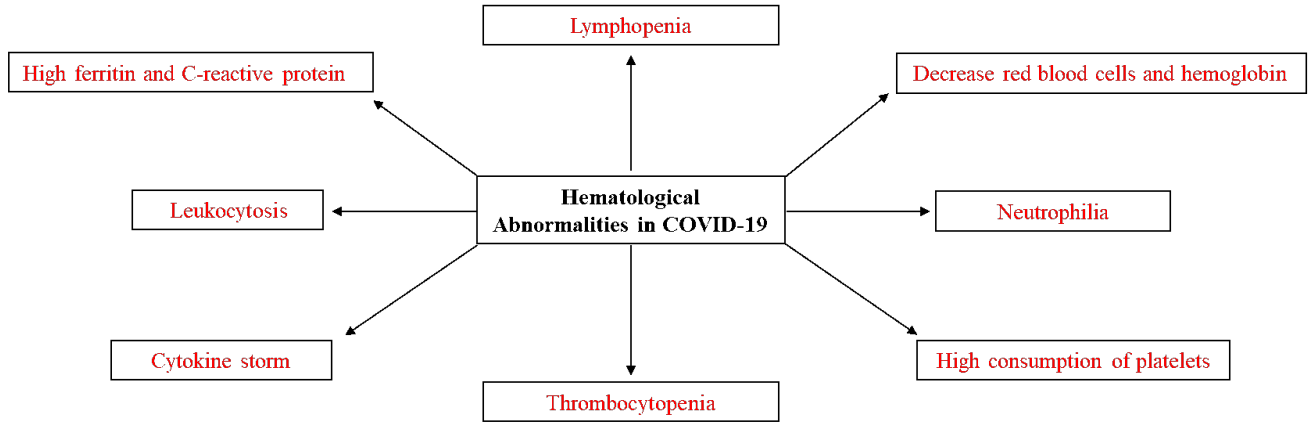

Figure 1: *Hematological alterations in patients with severe COVID-19.*

CONCLUSION

Future studies are needed to explain the role of hematological changes in the clinical severity of COVID-19 for an early prognosis of hospitalized individuals with severe conditions. In this study, it is evident that there are hematological alterations, mainly in non-survivor patients, changes such as lymphopenia, neutrophilia, leukocytosis, and thrombocytopenia are often found, in addition to the drop in hemoglobin and red blood cells, higher concentrations of ferritin and C-reactive protein, cytokine storm and platelet consumption. In this way, it's clear the relevance of collecting this laboratory information to understand the vulnerability of COVID-19 patients and how to identify the changes caused by the virus in order to obtain good early treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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