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REVIEW

Hematological Alterations in Patients with COVID-19

Alteraciones hematológicas en pacientes con COVID-19

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ABSTRACT

Currently, the global population is under siege from COVID-19, a disease caused by the SARS-CoV-2 coronavirus, which has been declared a pandemic by the World Health Organization. COVID-19 usually presents with mild respiratory symptoms but is also associated with less common and somewhat delayed clinical manifestations such as thrombotic events (arterial or venous), skin inflammation, vasculitis, and the development of pulmonary fibrosis. A literature review was conducted with the aim of characterizing hematological changes in patients during COVID-19. A total of 23 bibliographic references were reviewed, including books, journals, and websites from the Scielo and Infomed platforms. It was found that the main hematological alterations caused by COVID-19 include lymphocytopenia, increased D-dimer, thrombocytopenia, platelet deficiency, and thrombosis, all of which are favored by the cytokine storm.

Keywords: COVID-19; Lymphocytopenia; Cytokine Storm; Thrombosis.

RESUMEN

Actualmente la población mundial se encuentra asediada por la COVID-19, una enfermedad causada por el coronavirus SARS-CoV-2; y ha sido declarada por la Organización Mundial de la Salud como una pandemia. La enfermedad COVID-19 suele presentarse con síntomas respiratorios leves, pero también se asocia a otras manifestaciones clínicas menos frecuentes y algo más tardías, como fenómenos trombóticos (arteriales o venosos), inflamación cutánea, vasculitis, y el desarrollo de fibrosis pulmonar. Se realizó una revisión bibliográfica con el objetivo de caracterizar los cambios hematológicos en los pacientes durante la COVID-19. Se revisaron un total de 23 referencias bibliográficas entre libros, revistas y páginas web de las plataformas Scielo e Infomed. Se evidencia que las alteraciones hematológicas que provoca la COVID-19 son linfocitopenia, aumento de D-dímero y trombocitopenia, plaquetopenia y trombosis favorecida por la tormenta de citoquinas.

Palabras clave: COVID-19; Linfocitopenia; Tormenta de Citoquinas; Trombosis.

INTRODUCTION

In mid-December 2019, a series of cases attributed to a viral infection appeared in Wuhan, China, meeting clinical criteria for pneumonia with varying degrees of severity, including respiratory failure and severe hypoxemia.[1]

This infection was attributed to a new coronavirus species, a beta coronavirus different from the one that causes Severe Acute Respiratory Syndrome (SARS)[2] and Middle East Respiratory Syndrome (MERS-CoV).[3] This new microorganism was named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the WHO on February 11, and is the cause of COVID-19 (coronavirus disease 2019).[4]

On January 30, 2020, the World Health Organization (WHO) declared the 2019 coronavirus disease a public health emergency of international concern (PHEIC). On March 11, 2020, the WHO officially declared the pandemic.[5]

As of August 5, 2021, there have been around 201 million coronavirus (SARS-CoV-2) cases worldwide. The most affected countries are the US, in first place with 631,879, Brazil in second place with 560 801, and India in third place with 426 785.[6]

The United States tops the death toll with over 631 500 deaths, followed by Brazil with around 560 800.[7]

In Latin America and the Caribbean, the number of confirmed cases is 41 583 333 cases of COVID-19. Brazil is the region most affected by this pandemic, with around 20,1 million confirmed cases. Argentina ranks second, with approximately 5,03 million infected. Mexico, for its part, has registered a total of 2 978 330 cases. Among the countries most affected by the new coronavirus are Colombia, Peru, Chile, and Ecuador.[8]

As of August 3, Cuba has accumulated 422 614 positive cases. There have been 3 091 deaths (98 in one day), with a fatality rate of 0,73 % compared to 2,13 % worldwide and 2,59 % in the Americas.[9]

According to the CMHW, on August 3, the province reported the highest number of infections since the pandemic began, with 723 cases. In addition, six people from Villa Clara died. The municipalities with the highest incidence rates are Sagua la Grande (1 510,87), Santa Clara (1 307,28), and Corralillo (747,84). To date, this number has dropped to 50 infected per month.[10] These figures show a decline thanks to cooperation and compliance with the measures stipulated by the government.

It is transmitted through the air or contact with mucous membranes, and its infectivity is high, as carriers can spread the virus while asymptomatic. After a variable incubation period ranging from 3 to 10 days, it initially manifests with respiratory symptoms. About 80 % of patients develop paucisymptomatic or even asymptomatic symptoms. The remaining 20 % develop a clinical picture characterized by bilateral interstitial pneumonia leading to respiratory failure and an increased systemic inflammatory response with elevated inflammatory markers. The mortality rate of patients who develop this inflammatory picture ranges from 10 % to 20 %. COVID-19 is associated with other less frequent and somewhat later clinical manifestations, such as thrombotic phenomena (arterial or venous), skin inflammation, vasculitis, and the development of pulmonary fibrosis.[11]

Infection with SARS-CoV-2, which causes COVID-19, may initially present with nonspecific clinical findings, mainly respiratory. The virus binds to ACE-2 receptors, expressed on respiratory epithelial cells, from where it enters the body. Viral replication produces a response characterized in severe cases by dysregulation of inflammation and coagulation.

Among the hematological alterations caused by this infection, it was known from the outset that it was associated with lymphopenia, thrombocytopenia, and coagulation disorders, which were initially identified as disseminated intravascular coagulation (DIC), with pulmonary thromboembolism (PTE) being the most common. This increase in pulmonary thrombotic manifestations has been described in autopsies of patients infected with SARS-CoV and MERS-CoV in 2003 and 2012, respectively. None of these manifestations are unusual in viral pneumonia, which is often associated with an excessive inflammatory response with cytokine secretion.[12]

Based on studies conducted in China and other countries, the clinical hematology laboratory plays a vital role in providing the medical team with a series of prognostic markers useful in the disease's clinical evolution. Although information is limited in some cases, the available findings establish that hematological variables represent an essential tool in the management of affected patients.[13]

The degree of lymphopenia has been linked to the severity and mortality of the infection, particularly the decrease in T8 lymphocytes. As different descriptions of the syndrome emerged, it became evident that there was also a significant elevation of D-dimer, fibrinogen, factor VIII, factor V, and von Willebrand factor (VWF) in severe cases.[12]

In turn, erythrocyte sedimentation rate (ESR) is an acute-phase reactant defined as one of the complementary factors useful in predicting patients with critical progression.[13]

In January 2020, Cuba designed the National Strategic Plan to Combat COVID-19, which includes central government agencies, companies, the non-state sector, and the general population. As part of its protocol, specifically in Annex 2, the protocol consists of the complementary tests that should be indicated in each case. Complete blood count with differential and erythrocyte sedimentation rate top the list of complementary tests in both suspected and confirmed cases.[13]

COVID-19 is a global pandemic that has affected millions of people due to its high degree of virulence. SARS-CoV-2 infection causes a wide range of conditions in various body systems, including the respiratory, renal, cardiovascular, and even the nervous systems. These conditions are due to the pathophysiology of the virus, which causes an exaggerated immune response in the host, a cytokine storm, causing hematological

alterations, including disseminated intravascular coagulation (DIC).

Given the importance of understanding the hematological changes caused by COVID-19 in predicting patient outcomes, we decided to conduct this literature review to deepen our knowledge on the subject.

Objective: To characterize hematological changes in patients during COVID-19

DEVELOPMENT

Pathophysiology and immune response in SARS-CoV-2 infection

SARS is the severe stage of COVID-19 caused by SARS-CoV-2, a respiratory virus belonging to the Coronaviridae family, subfamily Orthocoronaviridae. It is a positive-polarity single-stranded RNA virus with a genome of 26 to 32 Kb and is part of the betacoronavirus group that causes respiratory infection in humans, transmitted mainly through mucosal contact.[11,14,15]

Once the virus enters the upper airways with mild or no symptoms, it develops several pathways, either by establishing itself in the lungs, making its way to the digestive tract, a combination of both, or other organs. It descends to the lungs through the tracheobronchial tree, infecting the ciliated epithelium and the pneumocytes. The primary receptor for the coronavirus is ACE2, although the virus also binds to two C-type lectins expressed on dendritic cells, DC-SIGN and LSIGN, and the DPP4 receptor. They are found in various cell types, such as non-ciliated bronchial epithelial cells, other upper respiratory tract epithelial cells, alveolar epithelial cells, and endothelial cells of blood vessels at this level. ACE2 receptors are also found in the myocardium, kidneys, liver, and central nervous system. The DPP4 receptor is also found in epithelial cells of the kidney, small intestine, liver, pancreas, and prostate, as well as in activated leukocytes.[11,14,16]

SARS-CoV-2 infection is characterized by three phases:[15]

- Phase 1 or early infection: characterized by anosmia, fever, dry cough, and constitutional symptoms as clinical manifestations, with biomarkers including lymphocytopenia, increased D-dimer levels, increased LDH levels, and increased cytokine levels.
- Phase 2 or pulmonary: dyspnea and tachypnea are the clinical manifestations, and biomarkers include decreased O2 saturation, increased D-dimer levels, and pulmonary infiltrates (CT).
- Phase 3 or severe hyperinflammation: clinical manifestations include acute respiratory distress syndrome (ARDS), septic shock, acute renal failure, acute heart failure, disseminated intravascular coagulation, and biomarkers include: a significant decrease in O2 saturation, a greater increase in D-dimers, increased coagulation times, increased ferritin, increased interleukin 6 (IL-6), tumor necrosis factor α (TNFα), PCR, and increased troponin levels.

In some patients with COVID-19, the virus can produce an aberrant immune response, in which the innate immune response mediated by proinflammatory cytokines plays a fundamental role, such as interleukin one beta (IL-1β), IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) (synthesized mainly by macrophages) and interferon gamma (IFN-γ) (generated by T lymphocytes and a stimulator of the previous cytokines). The excessive production of these cytokines produces the so-called "cytokine cascade". It leads to a hyperinflammatory response, responsible for the ARDS picture and biological changes characterized by a remarkable increase in C-reactive protein (CRP) and ferritin levels. The elevation of these acute-phase reactants is similar to that seen in hemophagocytic lymphohistiocytosis (HLH) or its secondary form, macrophage activation syndrome (MAS).[11,15,17]

Severe COVID-19 is accompanied by elevated lactate dehydrogenase (LDH) levels, lymphopenia, thrombocytopenia, and increased D-dimer.[11,15]

Activation of the IFN pathway slows viral replication and activates the adaptive immune response, generating an exacerbated increase in proinflammatory cytokines, called a "cytokine storm," resulting in increased levels of interleukins such as IL-6, IL-2, IL-7, G-CSF, IFN-γ, and TNF, which appear to be involved in lymphocyte apoptosis.[14,15,17]

CD4+ T lymphocytes promote the production of virus-specific antibodies by activating T-dependent B lymphocytes; CD8+ cells are cytotoxic and can directly eliminate infected cells. A decrease in TCD4+ cells is associated with lymphocyte uptake in the lungs and reduced cytokine and antibody production. This leads to severe pneumonia known as severe respiratory syndrome, which consists of inflammation, tissue damage, functional impairment of the lungs, multiple organ failure, shock, and, in severe cases, death.[14,15]

Cytokines and chemokines are responsible not only for the pulmonary inflammatory response but also for the inflammatory process of the blood vessel endothelium. The former is responsible for the viral pneumonia reported since the onset of cases, which is subsequently complicated by bacterial superinfection, making it more severe. In the latter, the microvasculature is affected with inflammation of the endothelium (endotheliitis), release of more inflammatory cytokines, production of fibrin from fibrinogen, platelet aggregation, and pulmonary microthrombosis and in other organs, as well as thrombosis in large vessels (some researchers have called this disseminated interstitial coagulation instead of disseminated intravascular coagulation). This new finding

suggests that another culprit may be more deadly than viral pneumonia itself. Coagulation disorders have been discovered that play an essential role in lethal COVID-19.

The cytokine storm triggered by the innate and adaptive immune response to SARS-CoV-2 infection is considered to be the cause of COVID-19's complications and lethality.

Hematological changes in patients with SARS-CoV-2 infection

The manifestations of SARS-CoV-2 infection occur mainly in the respiratory tract; however, they can involve other systems such as the hematopoietic system. People with comorbidities are at increased risk of complications, including fulminant myocarditis and disseminated intravascular coagulation.[14]

One of the mechanisms that distinguishes SARS-CoV-2 infection from other coagulopathies commonly seen in patients with severe infection is direct damage to endothelial cells. This leads to a massive release of endothelial cell components, such as VWF multimers and plasminogen activators. In patients with systemic inflammation, ADAMTS-13 levels are decreased, so VWF multimers cannot be degraded proportionally. This accumulation of multimers induces microvascular thrombosis. Furthermore, the release of plasminogen activator results in the generation of plasmin and may explain the excessive increase in D-dimer levels. However, there may be other effects, as coronavirus infections appear to be associated with the typical fibrinolytic system activation.

During the incubation period, usually between day 1 and 14, when there are no specific symptoms of the disease, leukocyte and lymphocyte counts are normal or slightly decreased.[5]

When viremia increases, SARS-CoV-2 mainly affects tissues that express high levels of ACE, such as the lungs, heart, and gastrointestinal tract. After symptoms start, approximately 7 to 14 days later, a significant increase in cytokines and inflammatory mediators begins, known as a "cytokine storm." This can induce lymphocyte apoptosis. It is at this point that lymphopenia appears significantly. The most common hematological findings are lymphopenia, neutrophilia, eosinophilia, mild thrombocytopenia, and, in some cases, thrombocytosis has been reported. Absolute neutrophil counts increase in the first few days after admission (> 5 x109 / 10^9/L in 14/40 cases) and begin to decline a week later.[5]

One of the tests used to support the diagnosis of the disease is a complete blood count, which shows altered cell counts, mainly leukocytes and platelets. Leukocytes may be decreased with total values in severe cases of < 2 x 109 /10^9/L. Lymphocytopenia is moderate or severe with absolute values of 0,5-1 × 109/L and < 0,5 × 109/L, respectively, and is associated with an increased risk of developing acute respiratory distress syndrome (ARDS) as well as a higher probability of severity and admission to the intensive care unit.[14]

Lymphocytes have been shown to express the ACE2 receptor on their surface; therefore, the virus can directly infect these cells and ultimately cause lysis. Activating these cytokines can induce atrophy of the lymphoid organs, including the spleen, leading to lymphocyte apoptosis.[5]

In a study of pseudovirus and live virus infection, SARS-CoV-2 was shown to infect T lymphocytes via a protein S-mediated fusion membrane receptor, and the EK1 peptide can inhibit that infection.[5]

Flow cytometry does not show a reversal in the CD4+/CD8+ ratio. However, studies suggest that SARS-CoV-2 may affect the function of CD4+ helper and regulatory T lymphocytes. A marked decrease in CD8+ cytotoxic T cells accompanies this hyperactivation.[5]

It has been shown that patients with severe disease suffer from lymphopenia (≤ 600 cells/mm^3), so far the evidence suggests a greater involvement of cytotoxic T lymphocytes (CD8+) in the acute stage; in advanced stages, when coinfection is present there is an increase in leukocytes.[15]

In peripheral blood smears, it is common to observe reactive lymphocytes with plasmacytoid characteristics. Neutrophils in patients with severe disease may have absolute values of 11,6 x 10^9 /L. The morphology reported in the granulocytic line includes hypergranulation, hyposegmentation, nuclear hypercondensation, and the possibility of hypersegmentation.[14]

In Italy, at the Fondazione Policlinico A. Gemelli in Rome, following observation of peripheral blood smears before antiviral and/or anti-inflammatory treatment, morphological abnormalities of neutrophils and hyperchromatic megathrombocytes have been reported in both cases of thrombocytopenia and thrombocytosis. The neutrophils show toxic granulation and agranular cytoplasmic areas. In addition, there are crescent-shaped cells and left shift with myelocytes and metamyelocytes, sometimes without nuclear segmentation, with pseudo-Pelger forms. Apoptotic cells are also observed. These changes disappear with the start of treatment.[5]

The study by Guan et al.[18] showed leukopenia in 33,7 %, lymphopenia in 83,2 %, and thrombocytopenia in 36,2 % of cases.

Wu et al.[19] showed an association between lymphopenia and the development of acute respiratory distress syndrome (ARDS).

Huang et al.[20] and Wang et al.[21] point to an association between lymphopenia and the need for admission to the intensive care unit.

Lymphocyte counts can be used to predict patient outcomes. A model based on two lymphocyte counts has been proposed: patients with less than 20 % on days 10-12 from symptom onset and less than 5 % between days

17-19 have the worst prognosis.[5]

About humoral immunity, it has been reported that, in the plasma of convalescent patients, B cells produce antibodies directed against the SARS-CoV-2 glycoprotein, specifically the S protein. Xueto CA et al. report that in patients with severe disease, there are higher levels of IgG and higher total antibody titers associated with a worse prognosis.[15]

Data related to platelet count are very heterogeneous; some have suggested an association with an unfavorable course of the disease, and may range between 100 000 and 150 000/mm^3.[14]

Thrombocytopenia is associated with the severity of COVID-19 infection. Qu et al.[22] showed that the platelet/lymphocyte ratio emerges as an independent prognostic factor and that the higher it is, the greater the cytokine storm due to platelet hyperstimulation.

Inflammation may be increased in patients with high blood pressure, diabetes, and obesity. All these conditions induce platelet hyperreactivity. It has been shown that platelets undergo changes in gene expression and function in patients with COVID-19, and also that, in critically ill patients admitted to the ICU for the disease, platelets show hyperaggregability with a much greater tendency to bind to monocytes than in patients with mild infection.[12]

This suggests a role for platelets in the pathophysiology of the disease and supports the introduction of antiplatelet agents in the treatment of these patients, although further studies are needed before this therapy can be used widely.

During the phase of severe hyperinflammation, there is a greater increase in D-dimers, increased coagulation times, increased ferritin, increased interleukin 6 (IL-6), tumor necrosis factor α (TNFα), PCR, and increased troponin levels.[15]

Finally, the possibility of finding antiphospholipid antibodies in patients with the disease has been raised. In fact, the possible relationship between ABO system antigens and COVID-19 infection has recently been suggested. Blood group A is more susceptible than other antigens in the system, suggesting a possible protective role for group O.

For years, it has also been known that there is a strong connection between bronchoalveolar coagulation and fibrinolysis and the pathogenesis of acute respiratory distress syndrome, in which intrapulmonary fibrin deposition occurs. Measurement of coagulation and fibrinolysis factors in bronchoalveolar fluid has shown that physiological anticoagulant factors and endogenous fibrinolysis are insufficient to balance intrapulmonary thrombin generation. Recently, it has been reported that elevation of factor V above the upper reference range is associated with a higher incidence of thrombosis in critically ill patients admitted with COVID-19.[12]

The central hematological abnormalities during COVID-19 are lymphocytopenia, increased D-dimers, and thrombocytopenia.

Pulmonary thromboembolism is the most common hematological alteration caused by COVID-19, in addition to its high lethality for patients who suffer from it. For these reasons, it has been decided to delve deeper into the topic of thrombosis due to COVID-19.

Coagulation disorders and COVID-19

Disseminated intravascular coagulation is a clinical condition secondary to underlying diseases, trauma, neoplasms, and sepsis. The viral infection caused by COVID-19 produces sepsis by activating a strong systemic inflammatory response that causes an imbalance in homeostasis.[14]

Recent evidence shows that the most severe clinical form of COVID-19 can be complicated by coagulation disorders, specifically a form of disseminated intravascular coagulation, which carries a high risk of thromboembolic disease.[5]

There is a clear relationship between inflammation and thrombosis, in which each process promotes the activation of the other, following a positive feedback system. Communication between the two occurs at the level of all components of the hemostatic system, including endothelial cells, platelets, coagulation proteins, natural anticoagulant systems, and fibrinolytic activity. Once activated, endothelial cells secrete procoagulant and antifibrinolytic factors, such as tissue factor (TF), von Willebrand factor (vWF), thromboxane A2, and tissue plasminogen activator inhibitors 1 and 2 (PAI 1; PAI 2) in endothelial cells, smooth muscle cells of the arterial wall, macrophages, and even circulating monocytes.[16,17]

Interleukin 6 (IL6) stimulates the synthesis of C-reactive protein (CRP), fibrinogen, and serum amyloid A in the liver. CRP amplifies the immune response in tissues by stimulating the replication of nuclear factor kB (NF-kB), which induces the production of leukocyte adhesion molecules and chemokines in endothelial cells, and has a synergistic action with bacterial lipopolysaccharides, inducing the tissue factor (TF) of monocyte production. Interleukin 1 (IL1) causes the synthesis of PAI 1 in endothelial cells, while interleukin 4 (IL4) stimulates the production of tissue plasminogen activator (t-PA) by monocytes. T lymphocytes stimulate monocytes that have become macrophages through the CD40 receptor, also known as CD154 and members of the tumor necrosis factor alpha (TNFα) family, and promote TF production. Platelets regulate the gene expression of CD154, which

causes the synthesis of FT by macrophages and smooth muscle cells.[16,17]

Hypoxia, present in patients with pneumonia, can stimulate thrombosis, not only through increased cell viscosity, but also through increased hypoxia-inducible factor (HIF-1/HIF-2). Alterations in the hemostatic system include changes in activated partial thromboplastin time (aPTT) and prothrombin time (PT), and fibrin degradation products (FDP) and D-dimer are moderately or markedly increased, mainly in patients with severe disease.[14]

Four fundamental factors promote thrombosis during infection. First, the storm of proinflammatory cytokines such as IL-1β and IL-6 stimulates FT expression in immune cells and activates the coagulation mechanism. Second, the fibrinolytic system is suppressed by decreased urokinase-type tPA activity and increased PAI-1 release. Third, platelets are activated by various proinflammatory cytokines and readily adhere to the damaged endothelium. Fourth, inflammation-induced endothelial damage further accelerates the thrombotic reaction. In addition, immobilization, mechanical ventilation, central venous access devices, and nutritional deficiencies increase the risk of venous thromboembolism and pulmonary embolism.[16,17]

Early diagnosis of pulmonary thromboembolism in COVID-19 patients with typical clinical manifestations (sudden deterioration of oxygenation, respiratory distress, or hypotension) is of vital importance for the survival of these patients. Although published data are minimal, it seems reasonable to think that D-dimer and its kinetics of increase, together with recommended imaging techniques, could provide helpful information for the investigation of deep vein thrombosis (DVT) and/or PTE.[5]

ICU patients usually have many thrombotic risk factors; however, the pathophysiology of what is currently known about COVID-19 further increases this risk. Possible causes directly related to COVID-19 include endothelial damage, microvascular occlusions/thrombosis, and autoimmune events.[5]

A meta-analysis of seven studies, involving 1,783 ICU patients without COVID-19, found the incidence of VTE in ICU patients to be 12,7 % (95 % CI 8,7-17,5 %). It should therefore be noted that critically ill patients admitted to the ICU are at high risk of VTE due to both individual patient-related risk factors (age, immobilization, obesity, personal or family history) family history of DVT, cancer, sepsis, respiratory or cardiac failure, pregnancy, stroke, trauma, or recent surgery) and ICU-specific risk factors (sedation, immobilization, vasopressors, or central catheters).[5]

Several studies have observed elevations in D-dimer in sick patients, which is more pronounced in the most severe cases (statistically significant data). Another retrospective study showed more pronounced elevations in D-dimer and prothrombin time in patients who required admission to the ICU, compared to patients who did not require ICU admission. A study published by Cui et al. reported the prevalence of thromboembolic disease in patients with severe COVID-19 admitted to the ICU at around 25 %, without the use of thromboprophylaxis, of whom 40 % died. Elevated D-dimer levels >1,5 µg/mL (normal range 0,0-0,5 µg/mL) predicted thromboembolic disease (TED) with a sensitivity of 85 %, specificity of 88,5 %, and a negative predictive value of 94,7 %. In another retrospective study by Tang et al. covering data from 183 patients with COVID-19, non-survivors had significantly higher levels of D-dimer ($p < 0,05$), fibrin degradation products (FDP) ($p < 0,05$), and prolonged PT and PTT ($p < 0,05$) compared to survivors. In addition, 71,4 % of non-survivors versus 0,6 % of survivors met the clinical criteria for DIC during the disease. Patients with severe disease had higher D-dimer and PDF values than those with milder manifestations ($p < 0,05$ for both comparisons).[5]

Recently, Ciceri et al.[23] have proposed the acronym MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) to designate this pulmonary thrombotic microangiopathy or in situ thrombosis.

Consistent with this pathophysiological hypothesis, fibrin thrombi have been found in small pulmonary arterial vessels in autopsies of patients who died from COVID-19. It is interesting to know the incidence of deep vein thrombosis (DVT) in patients with COVID-19 and PTE. According to the series, in patients with PTE, the presence of concomitant DVT varies between 35 % and 45 %.[14]

Coagulopathy associated with COVID-19 is a characteristic among patients who die. In a study of 449 patients with severe COVID-19, treatment with anticoagulation, mainly with low molecular weight heparin (LMWH), appears to be associated with a decrease in mortality at 28 days in the population that met criteria for sepsis-induced coagulopathy or had markedly high D-dimer levels.[5]

This is demonstrated by the initial autopsy results, which show widely dispersed clots in multiple organs: large vessel clots including deep vein thrombosis (DVT) in the legs and pulmonary embolism (PE) in the lungs, heart (where myocarditis also occurs), clots in the arteries causing strokes, and small clots in small blood vessels in organs throughout the body. This complicates the situation with multiple organ damage syndrome, shock, severe cardiac arrhythmias, neurological deterioration with involvement of the cardio-respiratory regulatory centers in the brain stem, making this condition irreversible and leading to death.[16]

Therefore, given the high risk of VTE, pharmacological thromboprophylaxis is mandatory in hospitalized patients with COVID-19 according to the recommendations of the ISTH (International Society on Thrombosis and Hemostasis). In this context, the risk of VTE should be assessed in all patients with acute illnesses admitted to

the hospital, and thromboprophylaxis should be administered to all these high-risk patients by standard clinical practice guidelines.[5]

In addition, all patients with COVID-19 undergoing heparin therapy should be routinely evaluated for heparin-induced thrombocytopenia (HIT) using the 4T score (thrombocytopenia, time to platelet count drop, thrombosis, other causes of thrombocytopenia). Although the incidence of HIT in this group of patients has not yet been determined, there is a potential risk due to immune dysregulation and massive inflammatory syndrome induced by viral infection.[5]

Due to the percentage of critical and severely ill patients who develop PTE and/or DVT, thromboprophylaxis should be administered to patients at risk of worsening and monitored for signs of severe symptoms (sudden deterioration in oxygenation, respiratory distress, or hypotension).

CONCLUSIONS

The hematological alterations caused by COVID-19 are lymphocytopenia, increased D-dimers, thrombocytopenia, troponin, tumor necrosis factor, and thrombocytopenia. The inflammation caused by the cytokine storm promotes thrombosis. COVID-19 frequently induces states of hypercoagulability with inflammation that increases levels of procoagulant coagulation factors and disrupts the normal homeostasis of vascular endothelial cells, resulting in microangiopathy, local thrombus formation, and a systemic coagulation defect that leads to extensive vessel thrombosis and major thromboembolic complications.

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CONFLICT OF INTEREST

None.

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