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CHAPTER 13

HEMATOLOGICAL SEQUELAE AND ALTERATIONS IN THE POST–SARS-COV-2 INFECTION SYNDROME: A LITERATURE REVIEW

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ABSTRACT

This article aimed to identify and discuss the main hematological sequelae associated with Covid-19 infection, caused by the SARS-CoV-2 virus. This study is a literature review addressing general aspects of the pandemic, characteristics of the etiological agent, and clinical manifestations of the disease, with emphasis on symptoms and post-infection sequelae. Particular attention is given to the impact of Covid-19 on the human hematological system. The analyzed studies indicate that, although significant progress has been made in understanding post-Covid-19 complications, there is still no definitive consensus regarding the extent and pathophysiological mechanisms of these sequelae. However, available evidence suggests that SARS-CoV-2 infection may trigger an exacerbated inflammatory response, characterized by excessive cytokine release, known as a "cytokine storm." Although this process plays a central role in immune defense, it may also lead to damage to healthy cells and tissues. In the hematological context, this inflammatory response has been associated with clinically relevant alterations, including immune-mediated disorders and hematological diseases, such as autoimmune hemolytic anemia.

Keywords: SARS-CoV-2; Symptoms; Hematological Sequelae.

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INTRODUCTION

The first country to identify cases of infection caused by the SARS-CoV-2 virus was China, at the end of 2019; however, due to the virus's high transmissibility, the disease spread rapidly, reaching several countries around the world, including Brazil. Covid-19 presents a broad spectrum of clinical manifestations, ranging from asymptomatic cases to severe forms, with the most frequently reported symptoms being fever, dry cough, and dyspnea. In addition to respiratory involvement, clinical evidence shows that infection by SARS-CoV-2 is associated with important hematological alterations, such as lymphopenia, coagulation dysfunctions, and exacerbated inflammatory responses, which correlate with greater severity and worse prognosis. In more severe cases, the disease may progress to bilateral pulmonary infiltration, acute respiratory distress syndrome (ARDS), respiratory failure, and multiple organ failure, including hepatic, cardiac, renal, and hematological involvement (Guan et al., 2020). These systemic alterations may persist after the acute phase of infection, contributing to the development of post–Covid-19 syndrome, characterized by prolonged clinical manifestations and a significant impact on hematological homeostasis.

Since the beginning of the pandemic, countless studies have been conducted to measure the sequelae resulting from Covid-19. Nevertheless, to date, it is not yet possible to precisely determine all the physical and functional damage that SARS-CoV-2 infection may cause in the long term. Evidence indicates that the most severe adverse effects are often associated with the need for invasive mechanical ventilation, which may result in physical, cognitive, and psychiatric impairments, negatively affecting the quality of life of individuals and their families. Additionally, it is observed that patients previously diagnosed with Covid-19 may, in the post-infection period, present complications involving the respiratory, neurological, cardiovascular, gastrointestinal, hematological, and urinary systems (Lira *et al*., 2021).

Given this context, the present study proposes a discussion on Covid-19, highlighting its main symptoms and sequelae, with emphasis on the dysfunctions triggered in the hematological system. Accordingly, the general objective of this work is to identify and describe the main hematological consequences associated with infection by SARS-CoV-2.

The study was developed through a literature review organized from bibliographic research. According to Cruz (2010), this type of research constitutes the initial stage of any scientific investigation, regardless of the problem under study, aiming to provide the researcher with prior knowledge of the existing scientific production on the topic.

Complementarily, Lakatos and Marconi (2010) define bibliographic research as one that encompasses all publicly available bibliography concerning the investigated subject, including standalone publications, bulletins, newspapers, magazines, books, studies, monographs, and theses, as well as other

means of communication. The development of this work was based predominantly on the analysis of scientific articles and recent publications in specialized journals that address the Covid-19 pandemic and its systemic repercussions, with special attention to hematological alterations.

OBJECTIVE

To investigate, through a literature review, the sequelae in the hematological system resulting from SARS-CoV-2 infection in patients recovered from the acute phase of Covid-19, considering its interface with different physiological systems in the context of post–Covid-19 syndrome, as well as to describe the main hematological alterations associated with this infection.

JUSTIFICATION

This research is justified by the need to systematize and deepen scientific knowledge regarding the hematological sequelae observed after Covid-19 infection. Although significant advances have been made in understanding the disease's pathophysiological mechanisms, the hematological repercussions associated with post–Covid-19 syndrome still demand more consistent and integrated investigation.

SARS-CoV-2 infection may trigger an exacerbated inflammatory response, characterized by the release of a cascade of immune system signaling proteins—especially cytokines and chemokines—responsible for intercellular communication among immune cells. Although this response is essential for controlling infection, its dysregulated activation may result in damage to healthy cells and tissues, favoring the development of clinically relevant complications, such as autoimmune diseases—exemplified by autoimmune hemolytic anemia.

Additionally, evidence indicates that the most severe adverse effects of Covid-19 are often associated with the need for invasive mechanical ventilation, which may lead to persistent alterations in multiple physiological systems, including the respiratory, neurological, cardiovascular, gastrointestinal, urinary, and hematological systems. In this context, the analysis of hematological sequelae becomes fundamental for understanding the magnitude of the disease's systemic impact, supporting clinical follow-up strategies, and contributing to the appropriate management of patients in the post-recovery period.

DEVELOPMENT

COVID 19

The pandemic caused by the novel coronavirus began on December 31, 2019, in the city of Wuhan, located in the People's Republic of China, following the identification of several cases of pneumonia of unknown etiology. In January 2020, the outbreak was officially confirmed, displaying rapid

global dissemination. The etiological agent responsible for the disease was named in February 2020 as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (PAHO, 2023).

With the accelerated expansion of Covid-19 worldwide, the World Health Organization (WHO) declared, in January 2020, a Public Health Emergency of International Concern (PHEIC), considered the highest level of alert according to the International Health Regulations. Subsequently, in March 2020, the disease was officially classified as a pandemic by the WHO (PAHO, 2023).

Covid-19 is defined as an infectious disease caused by the SARS-CoV-2 coronavirus. According to the Pan American Health Organization (PAHO, 2023), the main symptoms include fever, fatigue, and dry cough. However, additional clinical manifestations may also occur, such as loss of taste and/or smell, nasal congestion, conjunctivitis, sore throat and headache, myalgia, arthralgia, skin rashes, nausea, vomiting, diarrhea, chills, and dizziness.

Moreover, viruses of the *Coronaviridae* family may cause damage across multiple organ systems, including the respiratory, cardiovascular, gastrointestinal, central nervous, and genitourinary systems. Initial clinical manifestations may resemble influenza-like illnesses, with symptoms such as loss of smell and taste, evolving, in more severe cases, to acute respiratory failure, severe pneumonia, and death (Ribeiro *et al*., 2021). In line with these findings, the Secretariat of Primary Health Care (SAPS, 2020) describes common symptoms such as fever between 37 °C and 38 °C, cough, dyspnea, myalgia, fatigue, upper respiratory symptoms, and gastrointestinal manifestations, such as diarrhea.

Regarding the structural characteristics of SARS-CoV-2, it is a virus composed of a single RNA strand located inside a nucleocapsid. The virus is enveloped by a lipid membrane that contains different structural proteins, including envelope proteins and spike proteins, known as Spike (S) proteins, which are responsible for the characteristic crown-like appearance that gives rise to the denomination "coronavirus" (Araújo, 2020).

Complementarily, SARS-CoV-2 belongs to the family *Coronaviridae*, genus *Betacoronavirus*, and subgenus *Sarbecovirus*, presenting structural similarities with other human-pathogenic coronaviruses, such as SARS-CoV, the agent of Severe Acute Respiratory Syndrome, and MERS-CoV, the agent of Middle East Respiratory Syndrome. It is an enveloped virus, approximately spherical in shape, with non-segmented single-stranded RNA. The spike glycoprotein (S) plays a fundamental role in binding to cellular receptors and in evasion of the host's immune response (Khalil; Khalil, 2020).

Coronaviruses are classified as non-segmented, positive-sense single-stranded RNA viruses enveloped by a protein coat, composed mainly of the E protein. Their virions display rounded or oval morphology, with diameters ranging between 60 and 140 nm. Through electron microscopy, prominent surface projections are observed, corresponding to the spike glycoproteins of the Spike protein, which are responsible for the "corona" denomination (Brito *et al*., 2020).

Transmission of SARS-CoV-2 occurs primarily through the expulsion of viral particles by infected individuals, which are inhaled by others, penetrating the nasal mucosa, rich in cells that express the Angiotensin-Converting Enzyme 2 (ACE2) receptor. The virus uses this receptor to bind to host cells, hijack the cellular machinery, and promote its replication. If the immune system cannot contain the infection at this initial stage, the virus may advance through the lower respiratory tract and reach the pulmonary alveoli (Vieira *et al*., 2020).

As an acute respiratory infection, transmission occurs predominantly through respiratory droplets, secretions, and direct contact with infected individuals. Studies show that SARS-CoV-2 may remain suspended in the air for approximately three hours, depending on environmental conditions, and remain viable on plastic surfaces for up to 72 hours (Brito *et al*., 2020).

With regard to the clinical manifestation of infection, SARS-CoV-2 primarily affects the respiratory tract, possibly triggering respiratory failure and Acute Respiratory Distress Syndrome (ARDS). Nonetheless, Covid-19 should be considered a systemic disease, since it affects multiple organs and tissues (Mehta et al., 2020; Ribeiro et al., 2021).

In general, infection by SARS-CoV-2 induces an exacerbated inflammatory response capable of causing significant damage to the cardiovascular system, resulting in heart failure, arrhythmias, myocarditis, shock, and Takotsubo syndrome. These events may be associated both with the imbalance between high metabolic demand and low cardiac reserve and with the activation of thrombogenic processes. In the respiratory system, the disease may progress from mild flu-like illnesses to pneumonia and ARDS. Furthermore, systemic inflammation, characterized by excessive cytokine release, is associated with relevant laboratory alterations, such as elevated troponin, D-dimer, leukocytes, procalcitonin, ferritin, interleukin-6, lactate dehydrogenase, and C-reactive protein (Ribeiro et al., 2021).

Clinical progression of Covid-19 may occur over up to 16 days after a short incubation period in mild to moderate cases, and may extend up to 10 weeks in more severe situations, in which the outcome may be fatal (Vieira et al., 2020). The emergence of viral variants is also noteworthy, such as Omicron, identified in 2021, characterized by multiple mutations. In addition to this variant, Alpha, Beta, Gamma, and Delta variants remain in circulation (PAHO, 2023).

To identify SARS-CoV-2 infection, serological tests and molecular methods are used, with particular emphasis on Real-Time Polymerase Chain Reaction (RT-qPCR), considered the gold standard for viral detection because it enables real-time amplification of viral RNA. As complementary tools for clinical investigation of the disease, imaging exams such as chest X-ray and computed tomography are employed (Ribeiro *et al*., 2021).

MAIN SEQUELAE OF COVID-19

According to the Pró-Vida Program, developed by the Court of Justice of the Federal District and Territories (TJDFT, 2021), the main sequelae associated with Covid-19 include persistent fatigue, excessive tiredness, weakness, general malaise, dyspnea, breathing difficulty or shortness of breath, as well as pulmonary or renal fibrosis. Other frequently reported manifestations include headache, myalgia, cognitive impairments such as difficulty with reasoning, concentration and memory, sleep disturbances, depression, anxiety, and worsening of preexisting clinical conditions. Less frequently, alopecia, chest pain, palpitations, thrombotic events, dizziness, abdominal pain, and urinary alterations may also occur.

Corroborating these findings, Ramirez (2022) highlights that, even after clinical recovery from the acute phase of infection, it is common for patients to present, for a period exceeding 12 weeks, persistent symptoms such as intense fatigue, weakness, muscle pain, chronic cough, and loss of smell and/or taste. In the cardiovascular system, complications such as myocarditis, heart failure, arrhythmias, acute myocardial infarction, increased blood coagulation, and inflammation of the pericardium are observed.

In the respiratory system, patients may develop pulmonary stiffening, known as pulmonary fibrosis, a condition associated with dyspnea and reduced tissue oxygenation. In the renal system, episodes of acute kidney injury may occur. In the neurological domain, Covid-19 has been associated with alterations in taste and smell, persistent headache, anxiety and depression, insomnia, encephalitis, stroke, cerebral venous thrombosis, intracranial hemorrhage, mental confusion, dizziness, as well as the development of neurological syndromes such as Guillain–Barré syndrome and parkinsonian manifestations (Ramirez, 2022).

Additionally, dermatological alterations such as hair loss, blister formation, edema, and skin irritations have been described. In the gastrointestinal system, anorexia, nausea, gastroesophageal reflux, diarrhea, abdominal pain, abdominal distension, and the presence of blood in the stool may occur. Ophthalmological impairments have also been reported, including hemorrhagic or non-hemorrhagic conjunctivitis, eyelid hyperemia, optic neuritis, and alterations in corneal nerve fibers. In the endocrine system, thyroid inflammations, hyperglycemia in previously diabetic individuals, increased insulin resistance, and the onset of type 1 diabetes mellitus are noteworthy (Ramirez, 2022).

It is noteworthy that deficits in memory, language, and reasoning figure among the most prevalent post–Covid-19 sequelae, frequently associated with neurological manifestations such as headache, as well as the onset or worsening of anxiety and depression. Individuals previously infected may present neurological symptoms such as dizziness, paresthesias, and stroke, in addition to systemic manifestations such as fatigue, dyspnea, persistent inflammatory processes, weight loss, and reduced functional capacity. In the cardiovascular system, complications such as thrombosis, arterial hypertension, arrhythmias, and

myocardial infarction are reported, while metabolic and organic alterations such as diabetes mellitus, renal dysfunctions, gastroesophageal reflux, and constipation may also be present (Pinheiro, 2021).

It is believed that factors such as prolonged immobility, extended use of mechanical ventilation, and sedation during the acute phase of the disease contribute significantly to the development of long-term sequelae. Among these, gustatory deficits; dysfunctions of the musculoskeletal, cardiorespiratory, gastrointestinal, cutaneous, and urinary systems; as well as cognitive impairments, such as attention and memory deficits; and mood alterations stand out. Even in mild cases of Covid-19, persistent fatigue, dyspnea, tachycardia, loss of muscle mass, reduced functional capacity, and, in the long term, pulmonary dysfunction are observed (Leal, 2021).

HEMATOLOGICAL SEQUELAE OF COVID-19

Among the numerous sequelae associated with Covid-19, hematological alterations stand out for their high frequency and clinical relevance. In this context, hypercoagulable states are commonly described, as well as alterations in platelet, leukocyte, and erythrocyte counts. The main alterations observed in patients with more severe disease include neutrophilia, lymphopenia, prolonged prothrombin time, and elevated D-dimer levels (Ribeiro *et al*., 2021).

According to Tang *et al*. (2020), several hematological parameters have been widely used as auxiliary tools in monitoring the clinical course of patients infected by SARS-CoV-2, as they reflect both the systemic inflammatory response and the severity of infection. Among these parameters, the occurrence of leukocytosis and neutrophilia—frequently associated with the exacerbated inflammatory state—stands out, as well as the worsening of lymphocytopenia, considered an important prognostic marker in patients with Covid-19. Additionally, the development of thrombocytopenia has been recurrently described, being related to disease progression, systemic involvement, and increased risk of complications, particularly in more severe clinical cases.

It is common for patients affected by Covid-19 to present reduced total leukocyte count and, especially, circulating lymphocytes. Viral infection promotes a systemic increase in inflammatory mediators and proinflammatory cytokines, capable of triggering significant lymphopenia, defined by an absolute lymphocyte count (ALC) below 1.0×10^9/L. Beyond the quantitative reduction, morphological alterations in lymphocytes are also described, such as cellular heterogeneity, presence of lymphoplasmacytoid lymphocytes, and large granular lymphocytes, reflecting a state of exacerbated immune activation (Ribeiro *et al*., 2021).

Neutrophilia, in turn, is closely associated with cytokine release and the hyperinflammatory condition observed in Covid-19, playing a relevant role in the disease's pathophysiology. In patients admitted to intensive care units, neutrophilia may also be related to the occurrence of secondary bacterial

infections. From a morphological standpoint, neutrophils may present hyposegmented nuclei, chromatin with pro-apoptotic characteristics, and hypergranular cytoplasm, sometimes with hypogranular basophilic areas. These alterations reflect accelerated and disordered granulopoiesis, correlated with the systemic hyperinflammatory state (Ribeiro *et al*., 2021).

Another frequent finding in patients diagnosed with Covid-19 is a hypercoagulable state, evidenced mainly by elevated levels of D-dimer—a product of fibrin degradation—whose presence is associated with worse prognosis and increased mortality. It should be noted that both hospitalized patients and those under outpatient follow-up present increased risk for venous thromboembolism, and early and prolonged pharmacological thromboprophylaxis—especially with low-molecular-weight heparin—is recommended (Ribeiro *et al*., 2021).

Studies conducted with patients severely affected by Covid-19 have demonstrated a high prevalence of circulating autoantibodies in the post-infection period. A study conducted in 2021 revealed that about 50% of the patients evaluated presented approximately 15 distinct autoantibodies directed against autoantigens associated with autoimmune diseases, such as myositis and systemic sclerosis. Furthermore, approximately 25% of these individuals presented antinuclear antibodies, suggesting persistent autoimmune activation following SARS-CoV-2 infection (Figueiredo *et al*., 2021).

In addition to quantitative alterations in hematological parameters, studies have demonstrated morphological and functional modifications in different cellular populations of the immune system in patients affected by Covid-19. Among these alterations, changes in cell volume and functional profiles of monocytes stand out, especially in individuals with more severe clinical manifestations. These alterations reflect a state of exacerbated immune activation and may contribute to dysfunction of the innate immune response, favoring imbalance between inflammation and coagulation. In this context, an association of these cellular alterations with the development of hemostatic disorders, such as disseminated intravascular coagulation (DIC), is observed—a condition frequently related to worse prognosis and increased mortality in patients with Covid-19 (Tang *et al*., 2020).

Additionally, a significant increase in clot formation and in thrombotic events in patients severely affected by Covid-19 has been widely documented, configuring a systemic coagulopathy associated with viral infection. These hematological and vascular manifestations are mainly related to two central pathophysiological mechanisms: exacerbated release of proinflammatory cytokines, characterizing the so-called cytokine storm, and the direct interaction of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) receptors, widely expressed in endothelial cells and various tissues throughout the organism. This interaction contributes to endothelial inflammation, vascular dysfunction, and activation of the coagulation cascade, favoring thrombus formation and aggravating systemic involvement observed in the most severe cases of the disease (Tang *et al.*, 2020).

The cytokine storm consists of massive release of signaling proteins produced by immune cells and other cell types, which act as mediators of the immune response against the pathogen. However, when this response occurs in a dysregulated manner, cytokines begin to cause damage to uninfected cells and tissues, contributing to the development of persistent systemic and hematological sequelae (Figueiredo *et al*., 2021).

As a consequence of this exacerbated immunological process, severe autoimmune diseases may arise, such as Guillain–Barré syndrome, in which the immune system itself begins to attack structures of the nervous system. In the hematological context, autoimmune hemolytic anemia stands out, characterized by the production of immunoglobulins of the IgG and/or IgM type directed against antigens on the surface of erythrocytes, resulting in activation of the complement system and the reticuloendothelial system, with consequent hemolysis and hemoglobin levels below 10 g/dL (Figueiredo *et al*., 2021).

In patients affected by Covid-19, a significant impact on the hematopoietic system is also observed, with emphasis on persistent lymphopenia. In individuals who progressed to severe forms of the disease, there are reports of the development of autoimmune diseases, such as systemic lupus erythematosus. This phenomenon may be explained by oxidative stress induced by viral infections, which potentiates defects in DNA methylation mechanisms, leading to genomic hypomethylation, overexpression of the ACE2 protein, and increased viremia—favoring perpetuation of the inflammatory and autoimmune response (Figueiredo *et al*., 2021).

CONCLUSION

Covid-19, caused by the SARS-CoV-2 virus, has been consolidated as a disease with broad systemic impact, whose consequences extend beyond the acute phase of infection. Although the disease's initial mechanisms have been widely investigated, it has become increasingly evident that a significant number of recovered individuals present persistent clinical manifestations, characterizing post–Covid-19 syndrome. In this context, hematological alterations emerge as central components interlinked with different physiological systems, reinforcing the need for an integrated and in-depth approach to the topic.

In line with the proposed objective, this systematic review made it possible to investigate and describe, in a critical and organized manner, the main sequelae in the hematological system resulting from SARS-CoV-2 infection in patients recovered from the acute phase of the disease. The findings of the analyzed literature show that alterations such as lymphopenia, neutrophilia, thrombocytopenia, hypercoagulable states, prolonged prothrombin time, and elevated D-dimer levels are recurrent, especially in individuals who presented more severe clinical conditions. These alterations reflect impairment of the hematopoietic system and its close interface with the immune, cardiovascular, and inflammatory systems.

The discussed data demonstrate that these hematological dysfunctions are strongly associated with an exacerbated and dysregulated inflammatory response, mediated by excessive release of cytokines and chemokines. Although this mechanism is fundamental for viral control, its prolonged or inadequate activation contributes to tissue damage, endothelial dysfunction, activation of coagulation, and the emergence of autoimmune phenomena, such as autoimmune hemolytic anemia—corroborating the pathophysiological complexity of post–Covid-19 syndrome.

Additionally, evidence indicates that patients subjected to intensive interventions, such as invasive mechanical ventilation, present higher risk of persistent systemic sequelae, including long-lasting hematological alterations. These findings reinforce that Covid-19's impact is not limited to a single system, but results from a systemic imbalance involving multiple interdependent biological pathways.

Thus, this bibliographic review is justified in systematizing the available knowledge on post–Covid-19 hematological sequelae, contributing to understanding the role of the hematological system in clinical progression and prognosis of these patients. By integrating dispersed data from the literature, this study offers relevant scientific subsidies for clinical follow-up, planning of therapeutic strategies, and the development of future research—especially those aimed at the early identification of complications and improvement of the quality of life of affected individuals.

It is concluded, therefore, that scientific deepening on the hematological sequelae associated with Covid-19 is essential to understand the magnitude of the systemic impact of SARS-CoV-2 infection. This review not only consolidates existing knowledge but also highlights gaps that should be explored by longitudinal and multicenter studies, reaffirming its scientific relevance in the current context of health research.

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