Revista de Ciencias Médicas de Pinar del Río

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

REVIEW ARTICLE

Case study on hematological dysfunctions in patients with COVID-19

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Received: December 30, 2025
Accepted: December 31, 2025
Published: December 31, 2025

Citar como: Buitrón-Estévez JL, Medina-Santos EW, Gonzabay-Olivero D, Solís-Sánchez MI. Estudio de casos relacionados con disfunciones hematológicas en pacientes con COVID-19. Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(S2): e7050. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/7050

ABSTRACT

Introduction: COVID-19 pandemic has generated a multisystemic impact, including hematological alterations that complicate clinical prognosis and require specialized attention.
Objective: to describe the most frequent hematological alterations in patients with COVID-19 and their clinical relevance as prognostic indicators of severity and disease progression.
Methods: a systematic review of the scientific literature was conducted across various databases. The search was performed using an algorithm with keywords and Boolean operators, allowing the identification of relevant sources. The selected studies, after applying inclusion and exclusion criteria, were critically analyzed considering timeliness, methodological quality, and thematic relevance, and were integrated into the final synthesis of the review. The final selection included 44 articles, complemented by the analysis of 20 documented clinical cases.
Development: the reviewed literature showed that lymphopenia, neutrophilia, anemia, and thrombocytopenia are the most common alterations, with variable prevalence depending on disease severity. Pathophysiological mechanisms associated with lymphocytic apoptosis, neutrophilic proliferation, and endothelial dysfunction were identified. Biochemical studies reported significant variations in hemoglobin, leukocytes, and platelets, as well as alterations in blood glucose and creatinine. Therapeutic strategies included immunoglobulins, corticosteroids, anticoagulation, and immune plasma, reflecting diversity in clinical approaches. Evidence suggests that these alterations may serve as prognostic biomarkers and guide therapeutic decisions.
Conclusions: it is important to recognize hematological alterations as indicators of severity in COVID-19. Their early identification allows optimization of therapeutic strategies and improvement of clinical management. Further research is needed to clarify underlying mechanisms and consolidate current intervention protocols.

Keywords: COVID-19; Hematologic Diseases; Prognosis; Hematologic Tests.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a profound impact on global health. This virus binds to ACE2 receptors on respiratory endothelial cells to enter the body, triggering a range of nonspecific respiratory symptoms. In severe cases, viral replication provokes a dysregulated immune response that affects both inflammation and coagulation pathways.[1]

Belonging to the *Coronaviridae* family, SARS-CoV-2 is classified within four main genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*, with implications for both human and veterinary health. Additionally, post-COVID syndrome (PCS) has been characterized by persistent symptoms such as fatigue and cardiovascular issues, which may last weeks or months after initial recovery.[2,3]

Since its emergence in late 2019, the SARS-CoV-2 pandemic has significantly impacted global public health. Although initially recognized for its effects on the respiratory tract, recent studies have revealed that the infection can also cause a variety of hematological alterations. These abnormalities not only complicate the clinical picture but may also serve as important prognostic indicators of disease severity and outcomes.[4,5]

Scientific literature has documented several hematological alterations in patients with COVID-19. For example, significant disturbances in the hematopoietic system have been reported, including lymphopenia in 30–75 % of cases and neutrophilia in 38 %, particularly in patients with severe disease forms. Additionally, eosinophil reduction was observed in 52,9 % of cases, and anemia in up to 51 %, with higher prevalence among intensive care unit (ICU) patients.[6] Thrombocytopenia was reported in 57,7 % of patients, along with various morphological blood cell abnormalities—such as reactive lymphocytes and bilobed neutrophils—associated with poor disease prognosis.[7]

These hematological alterations present complex biochemical and morphological bases that manifest as diverse blood disorders.[8,9,10,11,12] Given this context, the present review aims to describe the most frequent hematological alterations in patients with COVID-19 and their clinical relevance as prognostic indicators of severity and disease evolution.

METHODS

Study Design

This work constitutes a systematic literature review conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to identify, analyze, and synthesize available evidence on hematological alterations in patients with COVID-19. The search period spanned from January 2010 to June 2024, encompassing both pre-pandemic studies on hematological dysfunctions in viral infections and those published during the SARS-CoV-2 pandemic. The review adopted a descriptive and comparative approach, integrating clinically and epidemiologically relevant findings for medical practice.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

Information Sources
The bibliographic search was performed in major biomedical and multidisciplinary databases: PubMed/MEDLINE, SciELO, ScienceDirect, Google Scholar, LILACS, and BVSALUD. These platforms were selected for their international coverage and relevance in disseminating scientific literature in Spanish, English, and Portuguese. Secondary references from bibliographies of relevant articles were also included, along with gray literature (theses, technical reports, institutional documents) provided they met methodological quality criteria and offered full-text access. Inclusion of gray literature broadened the evidence base and reduced publication bias, particularly for regional studies from Latin America.

Search Strategy
The search strategy employed a structured algorithm using keywords and Boolean operators. Terms included: "COVID-19" AND "hematological alterations," "SARS-CoV-2" AND "hematologic dysfunctions," "lymphopenia OR neutrophilia OR thrombocytopenia" AND "patients," and "hematological parameters" AND "COVID-19 prognosis." Boolean operators AND and OR were used to combine and expand results, while truncation and quotation marks refined precision. Articles in Spanish, English, and Portuguese were considered without geographic restriction to ensure comprehensive and representative coverage.

Included studies were published within the defined timeframe (2010–2024) and directly addressed hematological alterations in patients with COVID-19 or comparable clinical contexts. Original articles, systematic reviews, meta-analyses, and case reports with relevant data on hematological parameters, prognosis, and treatment were accepted. Duplicates, articles without full-text access, irrelevant publications, studies outside the temporal range, and those lacking verifiable clinical data were excluded. Rigorous application of these criteria ensured information validity and reliability.

Selection Process
The selection process followed PRISMA recommendations. Initially, approximately 500 records were identified across consulted databases. After duplicate removal and title/abstract screening, the sample was reduced to 225 potentially relevant articles. Full-text reading subsequently excluded studies lacking clinical or methodological relevance. Ultimately, 44 articles meeting established quality and relevance criteria were included.

Data Extraction and Analysis
Data extraction was performed systematically using an analysis matrix designed to collect key variables: author, publication year, study design, sample size and characteristics, hematological parameters assessed, main results, and conclusions. A qualitative synthesis of findings was conducted, integrating information into thematic categories (lymphopenia, neutrophilia, anemia, thrombocytopenia, coagulopathies). Where studies presented homogeneous quantitative data, an exploratory meta-analysis was considered; however, methodological and population heterogeneity limited this approach, leading to a comparative narrative synthesis instead. Integration of results enabled identification of common patterns, discrepancies, and knowledge gaps, offering a critical and updated perspective on the topic.

DEVELOPMENT

Research on hematological alterations related to COVID-19 has identified several factors and enzymes playing crucial roles in disease pathogenesis. Lymphocytes expressing angiotensin-converting enzyme 2 (ACE2) receptors on their surface can be directly infected by SARS-CoV-2,

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

leading to cellular lysis. This lysis may also be induced by high levels of proinflammatory cytokines such as interleukin (IL)-6, IL-2, IL-7, and other inflammatory mediators.[13,14]

In patients with severe COVID-19, elevated levels of enzymes such as lactate dehydrogenase (LDH) and creatine kinase (CK) have been observed, suggesting extensive tissue damage and hematological complications. These enzymes are considered important prognostic markers of disease severity. Furthermore, ACE2—regulated by inflammatory factors—is implicated in SARS-CoV-2–associated endothelial and coagulation dysfunction. The protease TMPRSS2, involved in spike protein activation, is also associated with heightened inflammation and increased risk of thrombotic complications in severe cases.[15,16]

Other relevant enzymes include glucose-6-phosphate dehydrogenase (G6PD), whose deficiency may predispose patients to hematological complications such as hemolytic anemia, and furin protease, whose inhibition could reduce viral replication and mitigate disease severity.[17] Enzymes play a significant role in hematological alterations, including their involvement in immune responses and coagulation disorders. Their relevance in the pathogenesis and treatment of conditions like leukemia and aplastic anemia may offer novel therapeutic strategies.[18]

Complementary studies have demonstrated hematological alterations in peripheral blood and bone marrow of patients with COVID-19. These changes—comparable to those observed in human immunodeficiency virus (HIV) infections—include hypercellularity, megaloblastic changes, and necrosis, suggesting significant hematopoietic system involvement in COVID-19 pathogenesis.[19,20]

Biochemical testing for COVID-19 detection and hematological assessment is fundamental for diagnosis and treatment. RT-PCR is the primary method for identifying specific viral genetic sequences in oral and nasal samples. This test is highly sensitive and accurate, enabling viral gene amplification and detection via fluorescent probes.[21] Rapid antigen tests detect viral surface proteins using reactive strips that show color changes upon antigen-antibody interaction. Antibody detection against SARS-CoV-2 via ELISA techniques allows evaluation of the patient's immune response and determination of infection phase.[22]

Regarding hematological alterations, early and accurate detection is crucial. The complete blood count (CBC) is a basic test measuring blood components—including red blood cells, white blood cells, and platelets—providing essential information on patient health status.[23,24] Detailed blood analyses enable identification of a wide range of hematological pathologies. Coagulation studies, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), are critical for assessing the hemostatic system and diagnosing conditions like hemophilia. These tests also include fibrinogen and D-dimer measurements, offering crucial insights into coagulation and fibrinolysis status.[25]

Comorbidities significantly influence hematological complications in the context of COVID-19.,[26] The most common alterations include anemia, neutrophilia, leukocytosis, lymphopenia, and eosinopenia, with thrombocytosis being the most frequent platelet-related abnormality. Studies have also reported morphological abnormalities in red and white blood cells and platelets.[27]

The comorbidity between hematological alterations and COVID-19 is notable: lymphopenia and neutrophilia are associated with severe COVID-19 cases, and anemia is common among ICU patients. Other chronic conditions—such as renal failure and rheumatoid arthritis—are also linked to anemia due to inadequate erythropoietin production.[28,29,30]

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

Therapeutic strategies for hematological alterations in COVID-19 patients encompass diverse approaches—from pharmacological treatments to complex interventions like gene therapy and transplantation. For thrombocytopenia, fondaparinux and heparin-based thromboprophylaxis are recommended in critically ill patients.[31] Guidelines for COVID-19–associated coagulopathy suggest thromboprophylaxis for all hospitalized patients, although the optimal anticoagulation regimen remains undefined.[32]

Gene therapy emerges as a promising option to correct specific genetic mutations, particularly in hereditary diseases like hemophilia. Hematopoietic stem cell transplantation is crucial for treating conditions such as leukemia and lymphoma, though it carries significant risks.[33]

Blood transfusions are essential for patients with severe anemia or thrombocytopenia, providing rapid relief and improving overall well-being. Palliative care also plays a vital role in enhancing quality of life for patients with terminal hematological diseases. Finally, convalescent plasma therapy has demonstrated efficacy in clinical trials for COVID-19, receiving authorization from the U.S. FDA and the European Union due to its benefits and minimal side effects.[34]

Ultimately, studying hematological alterations in COVID-19 patients is critical to understanding how the virus affects the hematopoietic system and how these changes influence clinical management. Although primary manifestations of COVID-19 concentrate in the respiratory tract, hematopoietic system involvement can lead to severe complications such as fulminant myocarditis and disseminated intravascular coagulation (DIC)—particularly in patients with comorbidities, thereby increasing mortality risk.[35,36,37]

The current state of research on hematological alterations in COVID-19 highlights the importance of these abnormalities as biomarkers for the diagnosis and management of the disease. However, there are still gaps in knowledge regarding the underlying mechanisms that cause these alterations and their direct relationship with disease severity, since the studies conducted so far have used diverse methodologies and study populations, making direct comparison of results difficult.[38]

Aro et al.,[33] note that hematological and laboratory parameters—including blood cell counts and morphology—are crucial for evaluating patients with COVID-19. These analyses can provide diagnostic clues, assess disease severity, predict clinical course, and monitor systemic complications, aiding physicians in treatment planning.

Villa and Lopez,[27] report that lymphopenia may present as moderate (absolute values of 0,5–1 × 10^9/L) or severe (<0,5 × 10^9/L), with the latter associated with higher risk of acute respiratory distress syndrome (ARDS). Their research provides a solid foundation for identifying and analyzing specific alterations—such as thrombocytopenia, lymphopenia, and coagulopathies—common in SARS-CoV-2–infected patients.[20]

According to data from reviewed cases, biochemical marker analysis shows significant variability among patients. Hemoglobin ranged widely from 3,3 to 9 g/dL (mean: 8,5 g/dL; SD: 2,67), indicating substantial interindividual differences. Leukocyte counts varied from 1,500 to 33,700/µL (mean: 11,715,67/µL; SD: 11,681,82). Platelet counts ranged from 9 to 267 × 10^3/µL (mean: 117,554 × 10^3/µL; SD: 114,91), suggesting variability in coagulation capacity.[39.40.41]

Population-based studies across Latin America and the Caribbean observed that approximately 60 % of hospitalized COVID-19 patients presented lymphopenia—a lymphocyte count reduction

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7050

associated with greater disease severity and unfavorable prognosis. These findings indicate lymphopenia may serve as a prognostic marker in patient assessment.[42]

Additionally, thrombocytopenia—defined as low platelet count—has been identified in around 30 % of patients with severe COVID-19. This finding correlates with increased risk of hemorrhagic and thrombotic complications, further complicating clinical management. The Pan American Health Organization (PAHO) emphasizes the importance of monitoring platelet levels in hospitalized patients to anticipate and manage potential complications.[43]

Regarding treatment frequency, our study identified a significant variety of therapeutic interventions, with immunoglobulin being the most common—administered in 13 % of cases. Comparative research has corroborated the frequent use of other specific treatments in similar populations, underscoring the need for diverse therapeutic approaches to address the complexities of these conditions, including systemic inflammation management, pharmacological treatment with ceftriaxone, azithromycin, and dexamethasone, immunomodulators, parenteral hydration, and insulin infusion depending on the patient's condition.[44]

CONCLUSIONS

Beyond respiratory compromise, COVID-19 induces significant hematological and coagulopathic alterations—including lymphopenia, neutrophilia, thrombocytopenia, anemia, and elevated D-dimer—that function as biomarkers of severity and prognosis. These findings, consistent with WHO and PAHO reports, are associated with increased morbidity and mortality and underscore the need for timely hematological evaluations. Pathophysiology involves lymphocyte apoptosis, endothelial dysfunction, coagulation cascade activation, and exacerbated immune responses, while SARS-CoV-2 interaction with ACE2 and TMPRSS2 represents a potential therapeutic target. Clinical and biochemical heterogeneity—with variations in hemoglobin, leukocytes, platelets, glycemia, and creatinine—alongside diverse symptomatology and therapeutic approaches, demands an integrated, multidisciplinary, and individualized management strategy. Accurate detection via RT-PCR, antigen, and antibody testing is essential for diagnosis and infection control. Comorbidities such as diabetes, hypertension, cardiovascular disease, COPD, or cancer increase the risk of severe complications and mortality, even affecting life expectancy in vulnerable populations. These findings reinforce the importance of ongoing research and inclusive strategies to optimize clinical management and reduce health inequities.

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