

Abnormal laboratory findings review in SARS-CoV-2 infection

Revisão sobre as alterações em exames laboratoriais na infecção pelo SARS-CoV-2

Revisión de hallazgos anormales de laboratorio en la infección por SARS-CoV-2

Received: 04/03/2022 | Reviewed: 04/10/2022 | Accept: 04/12/2022 | Published: 04/17/2022

Marcus Vinícius Alves Lima

ORCID: <https://orcid.org/0000-0002-0694-8498>
Bahiana School of Medicine and Public Health, Brazil
Estácio de Sá University Center of Bahia, Brazil
E-mail: marcuslima@bahiana.edu.br

Polliana Silva Rodrigues

ORCID: <https://orcid.org/0000-0003-4925-7838>
Estácio de Sá University Center of Bahia, Brazil
E-mail: pollirodrigues@yahoo.com.br

João Otávio Ferreira Pereira

ORCID: <https://orcid.org/0000-0003-0696-7848>
Estácio de Sá University Center of Bahia, Brazil
E-mail: octavio.joao@estacio.br

Caroline Felix da Silva Mota

ORCID: <https://orcid.org/0000-0002-8494-859X>
Estácio de Sá University Center of Bahia, Brazil
E-mail: carol_bff6@hotmail.com

Mônica Nascimento Bittencourt

ORCID: <https://orcid.org/0000-0002-2914-2016>
Estácio de Sá University Center of Bahia, Brazil
E-mail: monica_nascimentob@hotmail.com

Winnie Revilane de Melo Marques

ORCID: <https://orcid.org/0000-0001-5909-111X>
Estácio de Sá University Center of Bahia, Brazil
E-mail: winnie.marques@hotmail.com

Cristina de Jesus Gomes

ORCID: <https://orcid.org/0000-0001-6879-1513>
Estácio de Sá University Center of Bahia, Brazil
E-mail: cristinajotagomes@gmail.com

Luciana Machado de Castro

ORCID: <https://orcid.org/0000-0002-3976-5460>
Estácio de Sá University Center of Bahia, Brazil
E-mail: lucianam.castro@yahoo.com.br

Idalina Sá de Oliveira

ORCID: <https://orcid.org/0000-0002-2297-3490>
Estácio de Sá University Center of Bahia, Brazil
E-mail: idalinahsa@hotmail.com

Elinete de Jesus Bispo

ORCID: <https://orcid.org/0000-0002-0648-5008>
Estácio de Sá University Center of Bahia, Brazil
E-mail: elibispo32@hotmail.com

Ana Kerlei Afonso Silva

ORCID: <https://orcid.org/0000-0003-3076-3132>
Estácio de Sá University Center of Bahia, Brazil
Email: kerlei.ana@gmail.com

Laíza De Oliveira Almeida

ORCID: <https://orcid.org/0000-0002-8750-8135>
Estácio de Sá University Center of Bahia, Brazil
E-mail: layza.almeidaa@gmail.com

Rafael de Carvalho Barreiros

ORCID: <https://orcid.org/0000-0002-1338-3333>
Estácio de Sá University Center of Bahia, Brazil
E-mail: rafajas@hotmail.com

Tatiane dos Santos Silva

ORCID: <https://orcid.org/0000-0002-9313-3552>
Estácio de Sá University Center of Bahia, Brazil
E-mail: tatysilvasantos@icloud.com

Luciele Cristina Lange

ORCID: <https://orcid.org/0000-0003-2912-0076>

Stuart Laboratory, Brazil

E-mail: lucielelange_@outlook.com

Afrânio Ferreira Evangelista

ORCID: <https://orcid.org/0000-0001-8011-4128>

SENAI Institute of Innovation in Advanced Health Systems, Brazil

Estácio de Sá University Center of Bahia, Brazil

E-mail: afranio.biomedico@gmail.com

Abstract

COVID-19 can trigger damage to the function and integrity of multiple cells, tissue or organs. In the progression of clinical manifestations, laboratory biomarkers can be used as predictors of prognosis to support in clinical conduction. This study aims to evidence an updated review of the literature of changes in biochemical and hematological laboratory tests of individuals with COVID-19 from articles prospected from the SciELO, LILACS and PubMed databases. Although in severe clinical spectrums, especially in patients admitted to intensive care unit, tissue lesions are more intense and more evident laboratory changes, can be observed in general in patients infected with SARS-CoV-2 increased levels of transaminases, alkaline phosphatase, gamma glutamyl transferase, bilirubin, urea, creatinine, lactic dehydrogenases, amylase, lipase, troponins, NT-ProBNP, pro-BNP, as well as reduction of MCV and MCHC, lymphopenia, neutrophilia, eosinopenia, thrombocytopenia, and prolongation of PT and aPTT.

Keywords: COVID-19; SARS-CoV-2; Laboratory tests; Health teaching.

Resumo

A COVID-19 pode desencadear prejuízos na função e integridade de múltiplas células, tecidos e órgãos. Na progressão das manifestações clínicas, biomarcadores laboratoriais podem ser utilizados como preditores do prognóstico para auxílio na condução clínica. Este estudo tem como objetivo evidenciar uma revisão atualizada das alterações nos exames laboratoriais bioquímicos e hematológicos de indivíduos com COVID-19 a partir de artigos prospectados das bases SciELO, LILACS e PubMed. Embora em espectros clínicos mais graves, principalmente nos pacientes admitidos em UTI, as lesões teciduais sejam mais intensas e as alterações laboratoriais mais evidentes, podem ser observados de forma geral nos pacientes infectados pelo SARS-CoV-2 aumento dos níveis de transaminases, FA, GGT, bilirrubina, ureia, creatinina, LDH, amilase, lipase, cTnI, NT-ProBNP e pro-BNP, bem como redução dos índices hematimétricos VCM e CHCM, linfopenia, neutrofilia, eosinopenia, trombocitopenia e prolongamento do TP e TTPA.

Palavras-chave: COVID-19; SARS-CoV-2; Exames laboratoriais; Ensino em saúde.

Resumen

COVID-19 puede desencadenar daños en la función y la integridad de múltiples células, tejidos y órganos. En la progresión de las manifestaciones clínicas, se pueden utilizar los biomarcadores de laboratorio como predictores de pronóstico para ayudar en la conducción clínica. Este estudio tiene como objetivo evidenciar una revisión actualizada de los cambios en las pruebas bioquímicas y hematológicas de laboratorio de individuos con COVID-19 a partir de artículos prospectados de las bases de datos SciELO, LILACS y PubMed. Aunque en espectros clínicos más graves, especialmente en pacientes ingresados en UCI, las lesiones tisulares son más intensas y las alteraciones de laboratorio más evidentes, se puede observar en general en pacientes infectados con SARS-CoV-2 aumento de los niveles de transaminasas, FA, GGT, bilirrubina, urea, creatinina, LDH, amilasa, lipasa, cTnI, NT-ProBNP y pro-BNP, así como reducción de los índices hematimétricos VM y CHCM, linfopenia, neutrofilia, eosinopenia, trombocitopenia y prolongación de TP y TTPA.

Palabras clave: COVID-19; SARS-CoV-2; Pruebas de laboratorio; Enseñanza en la salud.

1. Introduction

COVID-19 is an infectious disease, etiologically associated with the SARS-CoV-2 virus, which caused one of the most relevant pandemics in history in the second decade of the 21st century. More than 490 million cases have been reported worldwide, with more than 6 million deaths. In Brazil, more than 30 million cases and 660,000 deaths associated with this infectious disease were reported (WHO, 2022).

It is a systemic disease that frequently affects the respiratory system, progressing to a pneumonic condition in 10 to 15% of infected individuals. High fever, cough, dyspnea, myalgia, headache, diarrhea, and nausea are the most frequent clinical manifestations, which arise four to fourteen days after exposure to the pathogen (Xavier, et al., 2020). In critical

conditions, diagnosed mainly in individuals with immune system disorders and/or metabolic or infectious comorbidities, multiple organ dysfunction and septicemia may occur (Lippi, et. al., 2020).

The clinical alterations evidenced in patients with COVID-19 result from the action of the virus on the target cells of the infection and the surrounding damage triggered by hyperactivation of the immune response (Brandão, et al., 2020). Adsorption, the first stage of pathogen-host interaction at the cellular level, is mediated by the interaction of the Spike protein (S), present in the viral envelope, with the cell receptor angiotensin-converting enzyme 2 - ACE-2, which may be expressed in alveolar and endothelial cells. This S-ACE-2 interaction may contribute to renal-angiotensin-aldosterone system dysfunction.

The stabilization of the s protein binding and penetration of the virus into the target cell involves the action of furin and TMPRSS2 proteases in the conformational alteration of the S protein and in membrane fusion or endocytosis, with the possibility of involvement of non-canonical pathways. After denaturation of genetic material and viral replication, the viruses can contribute to the activation of apoptosis and pyroptosis events (Almeida, et al., 2020).

The constant antigenic stimulus, due to the mechanisms of immune evasion, unveils a strong activation of the immune system with intense secretion of pro-inflammatory cytokines, as well as activation and recruitment of neutrophils, monocytes/macrophages and lymphocytes, which can trigger cardiovascular, pulmonary, hepatic, kidney and pancreatic damage (Cândido, 2021; Zancanaro, et.al., 2021).

Given the modulation of the immune response against antigenic stimulation by SARS-Cov2, COVID-19 may present in mild, moderate and severe clinical spectra. Understanding the biochemical and hematological changes associated with the dynamics of this viral infection may be useful for monitoring the patient, establishing the clinical prognosis and therapeutic management. This article evidences an updated synthesis of changes in laboratory tests triggered by SARS-Cov2.

2. Methodology

A narrative review was conducted from scientific articles published in the databases: Scientific Electronic Library Online (SciELO), LILACS (Latin American and Caribbean Literature in Health Sciences), the National Library of Medicine (NLM®) of the United States (PubMed) via Medical Literature Analysis and Retrieval System Online (Medline) and the National Center for Biotechnology Information (NCBI). Despite not using explicit and systematic methods, the narrative review on this theme is an appropriate strategy for the continuing education of health professionals, as it describes updates on the subject, enabling new approaches from different contextual points of view (Rother, 2007). The descriptors were used in Portuguese and in English language, combined with the boolean operator "and": coronavirus infection, COVID-19 and results or laboratory findings. In order to delimit the object of study, productions were selected in the form of articles published from 2020, a period that initiated the COVID-19 pandemic. The choice of papers was based on the consonance of the limits of the subjects to the objective of the study, excluding those who, despite appearing in the search result, did not specifically address the theme. From this initial analysis, secondary prospection of work was carried out based on bibliographic references and analysis of documents made available by health agencies.

3. Results and Discussion

In the natural history of SARS-Cov2 infection, functional or quantitative cellular and molecular alterations may occur in the different clinical spectra of COVID-19. Since the evolution of the disease is rapid and progressive, it is relevant to understand the dynamics of the reaction to the infectious process and the associated changes detected in laboratory tests (Chen, et al., 2020).

Although the consensus on the main clinical manifestation of patients infected with SARS-Cov2 is the picture of pulmonary inflammation, the degree of lung involvement and disease progression are variable. Thus, the hematological and biochemical parameters evidenced in laboratory tests of patients with varied clinical spectrums provide a dimension of tissue and cellular damage and are essential in the clinical conduct and prognosis of patients (Xavier, *et al.*, 2020; Liu, *et al.*, 2020). These laboratory changes are discussed below in a stratified manner.

Leukocyte laboratorial changes

In the initial phase of infection in asymptomatic individuals, the absolute number of leukocytes may be within the reference range (Xavier, *et al.*, 2020). In the evolution to the critical phase, leukocytosis, predominantly polymorphonuclear, with intensity directly associated with the severity of tissue damage is noted. Thus, the continuous increase in the quantity of leukocytes in an individual with COVID-19 in clinical monitoring should be interpreted as a biomarker of poor prognosis. (Paula, *et al.*, 2021; Pereira, *et al.*, 2021; Sun, *et al.*, 2020; Wang, *et al.*, 2020; Ye, *et al.*, 2020; Blomme, *et al.*, 2020; Guclu, *et al.*, 2020; Pirsalehi, *et al.*, 2021)

Neutrophilia can be triggered by hyperactivation of cellular components of the immune system and elevated secretion of pro-inflammatory cytokines, such as IL-1 β , IL-6, IL-8 and TNF-alpha, in the face of infection in several cells, including the immune system (Wang, *et al.*, 2020; Schulte-Schrepping, *et al.*, 2020). In addition to the activation and recruitment of neutrophils by the inflammatory environment generated, additional antigenic stimulation may occur due to secondary bacterial infections (Wang, *et al.*, 2020). These stimuli can develop the release of immature neutrophils from the bone marrow, potentiating the impairment of peripheral immune activity. Scientific evidence indicates that the neutrophil/lymphocyte ratio (NLR) can be considered a biomarker of severity for patients with COVID-19. According to Liu *et al.* (2020), the increase of one unit in the NRL ratio raises the risk of death by approximately 8%. Corroborating this finding, other studies have demonstrated leukocytosis with neutrophilia and major NLR in patients with severe clinical spectrums (Pereira, *et al.*, 2021; Ye, *et al.*, 2020).

In addition to the neutrophilic alteration, individuals with COVID-19 may have eosinopenia (Zhang, *et al.*, 2020; Chen, *et al.*, 2020; Tan, *et al.*, 2020). Eosinophils are important cells of the immune system to maintain homeostasis in the face of invasion by parasitic pathogens and may be activated in a marked inflammatory situation (Pereira, *et al.*, 2021). The reduction of these blood cells quantity could be related to the homing process for the injured anatomical sites or alteration in the production of this lineage in the leucopoiesis process, which may be directed to the production of other cells of the immune system (Coradi, *et al.*, 2021; Pereira, *et al.*, 2021). Among critically ill patients, more than 80% may present this laboratory finding (Tan, *et al.*, 2020).

For findings related to monocytes, the transient reduction of its total percentage in peripheral blood has also been observed in severe cases of COVID-19 (Quin, *et al.*, 2020; Zhou, *et al.*, 2020a; Payen, *et al.*, 2020). This change may occur due to *homing* to the injured tissues because in addition to the increase in pro-inflammatory cytokines, there is an increase in the secretion of CCL2 and CCL7, chemokines that can attract monocytes (Zhou, *et al.*, 2020b). In addition to the change in the absolute number in the blood, phenotypic and quantitative changes in monocytic subpopulations are noted. Despite the reduction of the non-classical monocytes' population in COVID-19, there is expansion of the HLA-DR^{hi}CD11c^{hi} inflammatory subpopulation in the moderate clinical spectrum. In severe conditions, monocytes present low HLA-DR expression and high expression of genes with anti-inflammatory properties, which may compromise the presentation of antigens to lymphocytes and subsequent activation and clonal expansion, as well as macrophage killing mechanisms. Thus, this change would be

related to a high risk of developing systemic complications and increased mortality from septic shock. (Silvin, *et al.*, 2020; Schulte-Schrepping, *et al.*, 2020).

Lymphocytic laboratorial changes

In viral diseases, lymphocytes play a primary role in the clearance of the pathogen. Due to clonal activation and expansion, they may be in greater quantity in peripheral blood. However, one of the hematological alterations in patients with COVID-19 is lymphopenia, whose intensity represents a biomarker of severity. The decrease in the number of lymphocytes in peripheral blood may be the result of infection of these cells by SARS-CoV-2, since lymphocytes have the ECA-2 receptor in its membrane, which interacts with the surface biomolecules of the viral structure, allowing adsorption and penetration of the pathogen (Cândido, 2021).

The subsets of CD4⁺ T lymphocytes, CD8⁺ T, B and *natural killer* (NK) are important for maintaining body homeostasis opposite various infectious or non-infectious diseases. Under infectious conditions, different pathogen classes can induce modulation of the immune response with divergent quantitative and phenotypic changes in lymphocytic subpopulations. In patients with COVID-19, a reduction in CD4⁺ T cells, CD8⁺ T cells, B cells and NK (Wang, *et al.*, 2020a) was observed. This lymphopenia can be caused by direct damage resulting from interaction with the viral particle, by surrounding damage due to inflammatory cytotoxic mediators or by the exudation of circulating lymphocytes to inflammatory tissues, especially the pulmonary site. When lymphopenia is evaluated in T lymphocyte subpopulations, CD8 lymphocyte depletion is related to the severe form of the disease, directly correlating to serum levels of inflammatory mediators (Zancanaro, *et al.*, 2021; Kratzer, *et al.*, 2020). Despite this quantitative change, these cytotoxic lymphocytes often exhibit an exhaustion phenotype with high expression of inhibiting receptors such as PD-1. This impairment of the cytotoxic potential of TCD8⁺ lymphocytes, especially the subpopulations of effector memory and terminally differentiated effector memory, contributes to the permanence of the infection since these cells play a crucial role in the destruction of virus-infected cells (Westmeier, *et al.*, 2020).

A systematic review conducted in 2021 revealed that 80% of clinical-based studies point to lymphopenia (35%-75%) as the most evident hematological alteration (Pereira, *et al.*, 2021). The constant evaluation of absolute lymphocyte count becomes extremely relevant in critical patient monitoring, since a measurement below $0.6 \times 10^9/L$ may be a biomarker suggestive of early admission to the intensive care unit (Wang, *et al.*, 2020b).

Erythrocytic laboratorial changes

SARS-CoV-2 also has mechanisms of infection in red blood cells, contributing to the severity of hypoxemia in patients with COVID-19 and, consequently, to damage to the lower respiratory tract. Binding with red blood cells can occur due to the likely interaction of the whole membrane protein band 3 with the Spike S1 protein of the virus, allowing the entry of the virus into the cell. This interaction may impair the transport of oxygen through red blood cells (Cosic, *et al.*, 2020; Khawaja, *et al.*, 2021).

Anemia and changes in iron metabolism observed in patients with COVID-19 seem to be related to red blood cell destruction due to systemic inflammatory condition, especially vascular, decreased oxygen transport caused by pulmonary involvement and the state of hyperinflammation with increased pro-inflammatory cytokines that may alter bone marrow response in erythropoiesis to interfere with the structure and variability of red blood cells size (Paula, *et al.*, 2021). Thus, erythrogram may show a reduction of 40% to 50% of hemoglobin in addition to the decrease in red blood cells and hematocrit (HCT) in patients with severe COVID-19. These findings of reduction of the mean cell/corpuscular volume (MCV) and mean cell hemoglobin concentration (MCHC) were observed in individuals who did not survive the infection. In addition, red cell

distribution width (RDW) is elevated compared to the group of patients with mild or moderate spectra (Guan, *et al.*, 2020; Huang, *et al.*, 2020). These parameters, combined with decreased lymphocytes and increased neutrophils, are revealed as predictors of severity and provide important information in hospital follow-up for therapeutic or supportive management (Kilercik, *et al.*, 2021).

Another hematological parameter that presents alteration in COVID-19 conditions is the erythrocyte sedimentation rate (ESR). This rate is commonly altered in inflammatory processes due to plasma protein increase. In SARS-CoV-2 infection, elevation can reach ranges between 15% and 85% (Lippi, *et al.*, 2020; Cândido, 2021).

Platelet laboratorial changes

Thrombocytopenia is the most common change in platelet series in COVID-19, whose intensity varies according to the severity of the clinical picture. Given the inflammatory environment generated, platelets may be reduced due to persistent activation by pro-inflammatory mediators, such as platelet activating factor, as well as through thrombin generated. In view of constant platelet consumption, a change also observed in patients with COVID-19 is the increase in the fraction of immature platelets which suggests an increase in the production of young platelets, which are more functional and may contribute to thrombotic events observed (Paula, *et al.*, 2021).

Some other changes in coagulation tests also point to the possibility of disseminated intravascular coagulation (DIC), such as prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), in addition to the increase in plasma values of fibrin degradation products (Vieira, *et al.*, 2020).

In critically ill patients, some studies show an increase in PT with values greater than 15 seconds, especially in patients who died (Tang, *et al.*, 2020; Zhou, *et al.*, 2020). A study conducted with 191 patients associated lethality with plasma d-dimer elevation ($> 1,000$ ng/mL) at hospital admission, as well as increased PT, observing signs of coagulopathy due to a 3-second increase in PT and a 5-second increase in aPTT (Zhou, *et al.*, 2020). The mean platelet volume (MPV) and platelet distribution width (PDW) are also elevated in individuals who develop the severe spectrum. This change may be due to higher platelet production in response to initial thrombocytopenia with consequent early release and increased serum amount of active young platelets. (Guclu, *et al.*, 2020)

Biochemical laboratorial biomarkers

Given the notability of performing laboratory monitoring for individuals with COVID-19 and how this information helps in directing the protocols to be adopted, biochemical markers can help in recognizing the injury or function damage caused to a given organ or system, since it is already known the normal blood levels of the interest metabolite. Thus, gathering evidence from the literature that characterizes the main biochemical markers of clinical interest used in the laboratory diagnostic routine for COVID-19 is of great importance.

Regarding biochemical parameters, significant differences were evidenced in patients who developed the severe condition of COVID-19. Some studies have shown that the values in the dosages of direct bilirubin, low-density lipoprotein (LDL), urea, creatinine, serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenases (LDH), C-reactive protein (CRP), ferritin, D-dimer and albumin levels showed statistically proportional variations in disease severity, and these biomarkers were predictors of a worse prognosis (Lv, *et al.*, 2021; Bastug, *et al.*, 2020; Wang, *et al.*, 2020; Lozano & Palacios, 2021; Maguire, *et al.*, 2020; Shah, *et al.*, 2020).

Kidney function biomarkers changes

In addition to the respiratory system, COVID-19 may target other organs and systems in our body, such as the renal system. The pathogenesis of kidney injury caused by SARS-CoV-2 infection can be explained by the direct impact of the virus on the renal parenchyma through the activation of ACE-2, which is also expressed in large quantities in renal cells, making these host cells of the virus. In addition, other mechanisms may be associated with kidney injury, such as cytokine storm and consequently hyperinflammatory conditions, as well as macrophage activation, lymphopenia and the generation of fibrin microthrombi, which can cause acute renal ischemia, followed by ischemic tubular necrosis due to urinary volume depletion and hypotension, resulting in decreased glomerular filtration and may develop a picture of acute renal failure (Santos & Mendonça, 2020; Chagas, et al., 2021; Ahmadian, et al., 2020).

In their review, Lima et al. (2022) demonstrated important complications due to the action of SARS-CoV-2, including proteinuria, hematuria, increased urea and creatinine in the blood and reduced glomerular filtration rate. This corroborates the study by Nogueira, Samuel et al. (2020) in which acute renal failure was one of the most cited manifestations along with laboratory alterations mentioned above, which are evidenced and more prevalent in patients with greater severity and in those who died.

In the face of kidney injury, articles report the increase in creatinine and serum urea, as well as the appearance of hematuria and proteinuria in the urine summary, such as a large prospective study conducted by Cheng et al. (2020) in China, with 701 cases of patients with COVID-19. In this study, the researchers stated that among patients with COVID-19, 44% had hematuria and proteinuria, however 26.7% had hematuria at the time of admission to the hospital.

According to the study by Chen, T. et al. (2020) proteinuria was found in 60.24% of patients with COVID-19. The study by Li et al. (2020) with 59 patients showed that 34% of patients had albuminuria on hospital admission and 63% developed proteinuria during their stay in the hospital. This elevation of proteinuria can be explained by virus replication in renal tubule podocytes. However, more detailed studies need to be conducted to prove this hypothesis (Lima, et al., 2022; Cheng, et al., 2020; Su, et al., 2020).

Liver and bile injury biomarkers changes

The liver is another organ that may be targeted by COVID-19 and the pathological mechanisms leading to liver injury include direct cytotoxicity of viral replication of SARS-CoV-2 in the liver, immunomodulated liver damage due to severe inflammatory response, hypoxic changes induced by respiratory failure, vascular changes due to coagulopathy, drug-induced liver injury, and exacerbation of pre-existing liver disease (Nardo, et al., 2020; Wang, et al., 2020; Kucharski, et al., 2020)

In patients with COVID-19, the elevation of hepatic transaminases SPGT and SGOT was observed, which may be accompanied by slightly increased total bilirubin, while elevations of cholestatic liver enzymes (alkaline phosphatase and gamma glutamyl transferase) are rarer or less evident. When present, they may suggest cholestasis induced by systemic inflammatory response at hepatocellular or canalicular level or an important bile duct lesion at the later stage of the disease (Nardo, et al., 2020)

The study by Wang et al. (2020) suggests the possibility of observing that liver enzymes present statistically significant alterations due to the lesions caused by SARS-CoV-2 infection in hepatocytes, generating tissue depletion. This aspect was more related to those individuals with severe COVID-19 with the increase in liver marker indices such as SGPT, SGOT and GPT (Wang et al., 2020). This is because when entering the cell, SARS-CoV-2 promotes tissue injury, thus generating a deregulation of its protein production. The picture of viral pneumonia that usually occurs in severe complications of the disease significantly uses these markers to predict prognosis (Guneyusu, et al., 2020; Maguire, et al., 2020).

Other studies show normal levels of liver function markers in hospitalized individuals, however, more than half of the studied population presented elevation in at least one of the enzymes during hospitalization (Saini, et al., 2020), and may also use PCR in joint analysis of IL-6 as inflammatory biomarkers in COVID-19 patients with normal liver function test (Hwaiz, et al., 2021).

Cardiac biomarkers changes

Although COVID-19 triggers predominantly respiratory symptoms, the severe form of the disease is correlated with cardiovascular complications that contribute to its worse prognosis. Patients with COVID-19 have the potential to develop a series of cardiovascular complications, such as arrhythmia, heart failure, myocardial injury or even death from cardiac arrest (Chen, et al., 2020; Tajbakhsh, et al., 2021). In this sense, the risk of death by COVID-19 can be evaluated through the investigation of myocardial injury biomarkers, together with the crossing of epidemiological data of patients such as advanced age and presence of comorbidities (Tajbakhsh, et al., 2021).

Although there is still no exact mechanism that explains how SARS-CoV-2 infection can cause myocardial injury, studies show that the probable mechanism of cardiac injury is due to systemic inflammation, hypoxia or through direct cell injury caused by the entry of the virus into cardiomyocytes. Because they have a high expression of the Enzyme ACE-2, which is closely related to blood pressure control, they are more vulnerable to SARS-CoV-2 infection, which can cause viral myocarditis and increase the formation of fibrosis (Babapoor-Farrokhran, et al., 2020; Tajbakhsh, et al., 2021).

Regarding laboratory biochemical tests, the main biomarkers of cardiac injury that are elevated in SARS-CoV-2 infection are cardiac troponin I (cTnI) and markers of myocardial dysfunction, such as n-terminal fragment of the natriuretic peptide type B (NT-ProBNP) and the pro-peptide natriuretic-B (pro-BNP) (Egidio et al., 2020). Studies have shown that cardiac troponin I levels were elevated in patients with the severe form of the disease compared to the moderate form and that 11.8% of patients who did not have preexisting heart disease and who died of COVID-19 had increased levels of cTnI (Lippi, et al., 2020c; Han, et al., 2020; Tajbakhsh, et al., 2021).

In a study conducted in 2020, Verdoni et al. demonstrated that 55% of the patients with COVID-19 investigated had high levels of cardiac troponin and all had high levels of pro-BNP. Similarly, Deng et al. in 2020 demonstrated that, even in conditions of severe pulmonary impairment, the elevation of these biomarkers peaked only in the week preceding the death of these patients, showing that the increase of these biomarkers may be an indicator of poor prognosis of the disease. Thus, the markers of cardiac injury in COVID-19 mentioned in this study are closely related to disease progression, as well as can serve as a basis for prognostic evaluation of the disease and adoption of better forms of treatment.

Pancreatic biomarkers changes

The ability of the SARS-CoV-2 to use the ACE2 enzyme as a gateway to invade human cells is a key mechanism for the involvement of various organs of the human body during infection and the same occurs with pancreatic cells. Research studies shown that infection of the virus in pancreatic cells can provoke an inflammatory process resulting in increased levels of the lipase and amylase enzymes (Cordero, et al., 2020; Liu, et al., 2020). However, in severe cases it is difficult to determine whether pancreatitis or pancreatic injury is the result of the cytopathic effect of the virus on the cells of the pancreas or result of the exacerbated and systemic inflammatory process observed in the disease (Cordero, et al., 2020).

According to a study conducted with patients hospitalized by COVID-19, of the 71 investigated, 9 (12.1%) had a hyperlipasemia 2 or 3 times higher than the recommended limit, but without observation of cases of acute pancreatitis or association with poor prognosis of the disease (Mcnabb-Baltar, et al., 2020). On the other hand, Wang et al. (2020) observed in

their study that 17% of the patients investigated had acute pancreatitis, along with increased lipase and amylase. Together, this evidence strengthens the idea discussed by some authors that SARS-CoV-2 infection may cause mild pancreatic injury or enzymatic changes that may be related to its cytopathic effect or systemic inflammation (Wang, et al., 2020; McNabb-Baltar, et al., 2020; Egidio, et al., 2020).

4. Final Considerations

The interaction of the SARS-CoV2 virus with human cells can lead to systemic disturbances in the host with quantitative and functional alterations of molecular components and blood cells, which may be useful as prognostic biomarkers in monitoring the evolution of COVID-19. Although the intensity of biochemical and hematological changes are related to the severity of the clinical spectrum, can be evidenced in general: lymphopenia, neutrophilia (with increased neutrophil/lymphocyte ratio) and eosinopenia; Elevated RDW with reduced hemoglobin, MCV and MCHC; thrombocytopenia with elevation of the d-dimer, prolongation of PT and aPTT; and increased levels of SGPT, SGOT, AP, GPT, bilirubin, urea, creatinine, LDH, amylase, lipase, cTnI, NT-ProBNP and pro-BNP. The conduction of new research studies may contribute to the understanding of the dynamics of other laboratory biomarkers in the evolution of COVID-19.

References

- Ahmadian, E., Abediazar, S., Khatibi, S. M. H., Soofiyan, S. R., Abediazar, S., Shoja, M. M., Ardalan, M., & Vahed, S. Z. (2020). COVID-19 and kidney injury: Pathophysiology and molecular mechanisms, *Rev Med Virol*, 31 (3), 1-13.
- Almeida, J. O., Oliveira, V. R. T., Avelar, J. L. S., Moita, B. S., & Lima, L. M. (2020). Covid-19: Fisiopatologia e alvos para intervenção terapêutica, *Revista Virtual de Química*, 12 (6), 1464-1497.
- Babapoor-Farrokhraha, S., Gillb, D., Walkerb, J., Rasekhic, R. T., Bozorgnia, B., & Amanullah A. (2020). Myocardial injury and COVID-19: possible mechanisms, *Life Sciences*, 253, 1-4.
- Batschauer, A. P. B., & Jovita, H. W. (2020). Hemostasia e COVID-19: fisiopatologia, exames laboratoriais e terapia anticoagulante, *Revista Brasileira de Análises Clínicas*. 52(2), 138-42.
- Bastug, A., Bodur, H., Erdogan, S., Gokcinar, D., Kazancioglu, S., Kosovalı, B. D., Ozbay, B. O., Gok, G., Turan, I. O., Yilmaz, G., Gonen, C. C., & Yilmaz, F. M. (2020). Clinical and laboratory features of COVID-19: Predictors of severe prognosis, *International immunopharmacology*, 88, 2020.
- Blomme, S., Smets, L., Ranst, M. V., Boeckx, N., & Laer, C. V. (2020). The influence of COVID-19 on routine hematological parameters of hospitalized patients, *Acta Clinica Belgica*, 77 (2), p. 241-246.
- Brandão, S. C. S., Godoi, E. T. A. M., Ramos, J. O. X., Melo, L. M. M. P., & Sarinho, E. S. C. (2020). COVID-19 grave: entenda o papel da imunidade, do endotélio e da coagulação na prática clínica, *Jornal Vascular Brasileiro*, 19, 1-11.
- Cândido, R. F. L. (2021). Alterações hematológicas associadas à COVID-19 em pacientes sintomáticos [Monografia, Universidade Federal do Rio Grande do Norte]. Repositório Institucional UFRN. <https://repositorio.ufrn.br/handle/123456789/43240>
- Chagas, G. C. L., Rangel, A. R., Noronha, L. M., Silva Junior, G. B., Meneses, G. C., Martins, A. M. C., & Daher, E. F. (2021). Covid-19 e os rins: uma revisão narrativa, *Rev. Bras. Saúde Matern. Infant*, 21 (2), 383-392.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, 395 (10223), p. 507-513.
- Chen, R., Liang, W., Jiang, M., Guan, W., Zhan, C., Wang, T., Tang, C., Sang, L., Liu, J., Ni, Z., Hu, Y., Liu, L., Shan, H., Lei, C., Peng, Y., Wei, L., Liu, Y., Hu, Y., Peng, P., Wang, J., Liu, J., Chen, Z., Li, G., Zheng, Z., Qiu, S., Luo, J., Ye, C., Zhu, S., Liu, X., Cheng, L., Ye, F., Zheng, J., Zhang, N., Li, Y., He, J., Li, S., & Zhong, N. (2020). Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. *Chest*, 158 (1), 97-105.
- Cheng, Y., Luo, R., Wang, K., Zhang, M., Wang, Z., Dong, L., Li, J., Yao, Y., Ge, S., & Xu, G. (2020). Kidney disease is associated with in-hospital death of patients with COVID-19, *Kidney International*, 97(5), 829-838.
- Coradi, C., & Vieira, S. L. V. (2021). Alterações leucocitárias em pacientes com COVID-19 observadas em extensão de sangue periférico, *Research, Society and Development*, 10 (11), p. 1-15.
- Cordero, P. M., Crespo, D. O., Caceres, W. S., Choez, K. M., Naunay, D. C., Davila, C. S., Carrillo, A. O., Morocho, G. C., & Calero, J. R. (2020). Lesión pancreática causada por Covid-19: ¿es la diabetes una secuela de la infección?, *Diabetes Internacional*, 12 (1), 34-38, 2020.

- Cosic, I., Cosic, D., & Loncarevic, I. (2020). RRM prediction of erythrocyte band 3 protein as alternative receptor for SARS-CoV-2 virus, *Applied Sciences*, 10 (11), p. 1-9.
- Deng, Q., Hu, B., Zhang, Y., Wang, H., Zhou, X., Hu, W., Cheng, Y., Yan, J., Ping, H., & Zhou, Q. (2020). Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China, *International Journal of Cardiology*, 311, 116-121.
- Egidio, A. N., Campos, B. N., Junqueira, C. F. S., Martins, F. R., Fabri Junior, J., Rodrigues, J. F., Siqueira, L. G. G., Oliveira, L. R. B., Ferreira, M. B. S., Antunes, V. R. M., & Torres, V. P. (2020). Implicações Cardiovasculares na Covid-19: Uma Revisão Sistemática, *Brazilian Journal of Development*, 6 (10), 82111-82128.
- Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S. C., Du, B., Li, L., Zeng, G., Yuen, K. Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., Li, S., Wang, J., Liang, Z., Peng, Y., Wei, L., Liu, Y., Hu, Y., Peng, P., Wang, J., Liu, J., Chen, Z., Li, G., Zheng, Z., Qiu, S., Luo, J., Ye, C., Zhu, S., & Zhong, N. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China, *The New England Journal of Medicine*, 382 (18), p. 1708-1720.
- Guclu, E., Kocayigit, H., Okan, H. D., Erkorkmaz, U., Yurumez, Y., Yaylaci, S., Koroglu, M., Uzun, C., & Karabay, O. (2020). Effect of COVID-19 on platelet count and its indices, *Revista da Associação Médica Brasileira*, 66 (8), 1122-1127.
- Han, H., Xie, L., Liu, R., Yang, J., Liu, F., Wu, K., Chen, L., Hou, W., Feng, Y., & Zhu, C. (2020). Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China, *Journal of Medical Virology*, 92 (7), 819-823.
- Huang, Y., Tu, M., Wang, S., Chen, S., Zhou, W., Chen, D., Zhou, L., Wang, M., Zhao, Y., Zeng, W., Huang, Q., Xu, H., Liu, Z., & Guo, L. (2020). Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A retrospective single center analysis, *Travel medicine and infectious disease*, 36, 1-3.
- Hwaiz, R., Merza, M., Hamad, B., Hamasalih, S., Mohammed, M., & Hama, H. (2021). Evaluation of hepatic enzymes activities in COVID-19 patients, *International Immunopharmacology*, 97, 1-4.
- Khawaja, U. A., Shamsoddin, E., Desideri, L. F., & Tovani-Palone, M. R. (2021). Infecção de hemácias por SARS-CoV-2: novas evidências, *Einstein*, 19, p.1-2.
- Kilercik, M., Demirelce, O., Serdar, M., Mikailova, P., & Serteser, M. (2021). A new haematocytometric index: Predicting severity and mortality risk value in COVID-19 patients, *Plos One*, 16 (8), p.1-19.
- Kratzer, B., Trapin, D., Ettl, P., Körmöcz, U., Rottal, A., Tuppy, F., Feichter, M., Gattinger, P., Brorochova, K., Dorofeeva, Y., Tulaeva, I., Weber, M., Grabmeier-Pfistershammer, K., Tauber, P. A., Gerdov, M., Muhl, B., Perkmann, T., Fae, I., Wenda, S., Fuhrer, H., Henning, R., Valenta, R., & Pickl, W. F. (2020). Immunological imprint of COVID-19 on human peripheral blood leukocyte populations, *Allergy*, 76 (3), p. 751-765.
- Kucharski, A. J., Russell, T. W., Diamond, C., Liu, Y., Edmunds, J., Funk, S., & Eggo, R. M. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *The lancet Infectious Diseases*, 20 (5), p. 553-558.
- Li, Z.; Wu, M.; Yao, J.; Guo, J.; Liao, X.; Song, S.; Li, J.; Duan, G.; Zhou, Y.; Wu, X.; Zhou, Z.; Wang, T.; Hu, M.; Chen, X.; Fu, Y.; Lei, C.; Dong, H.; Xu, C.; Hu, Y.; Han, M.; Zhou, Y.; Jia, H.; Chen, X.; Yan, J. (2020). Caution on Kidney Dysfunctions of COVID-19 Patients, *MedRxiv*, <https://doi.org/10.1101/2020.02.08.20021212>
- Lima, A. A., Almeida, A. G. C. S., Nunes, I. C. M., Sarmiento, P. A., & Alves, W. T. B. P. (2022). Complicações renais resultantes da infecção por SARS-CoV-2 em pessoas hospitalizadas com COVID-19: revisão de escopo, *Pesquisa, Sociedade e Desenvolvimento*, 11 (1), 1-15.
- Lippi, G., Plebani, M., & Henry, B. M. (2020). Thrombocytopenia is associated with severe coronavirus disease 2019(COVID-19) infections: A meta-analysis. *Clinica Chimica Acta*, 506, 145-148.
- Lippi, G., & Plebani, M. (2020). Laboratory abnormalities in patients with COVID-2019 infection, *Clinical Chemistry and Laboratory Medicine*, 58 (7), p. 1131-1134.
- Lippi, G., Lavie, C. J., & Sanchis-Gomar, F. (2020). Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis, *Progress in Cardiovascular Diseases*, 63 (3), 390-391.
- Liu, Y., Du, X., Chgen, J., Jin, Y., Peng, L., Wang, H. H. X., Luo, M., Chen, L., & Zhao, Y. (2020). Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19, *Journal of Infection*, 81 (1), 6-12.
- Liu, F., Long, X., Zhang, B., Zhang, W., Chen, X., & Zhang, Z. (2020). ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection, *Clinical Gastroenterology and Hepatology*, 18 (9), 2128-2130.
- Lozano, Y., & Palacios, E. V. (2021). Factores asociados a la hospitalización de pacientes con COVID-19 en la Unidad de Cuidados Intensivos de una clínica em 2020. *Horizonte Médico*, 21 (1), e1379, <https://doi.org/10.24265/horizmed.2021.v21n1.09>.
- Lv, Z., Wang, W., Qiao, B., Cui, X., Feng, Y., Chen, L., Ma, Q., & Liu, X. (2021). The prognostic value of general laboratory testing in patients with COVID-19, *Journal of clinical laboratory analysis*, 35 (2), 1-7.
- Maguire, D., Woods, M., Richards, C., Dolan, R., Veitch, J. W., Sim, W. M., Kemmett, O. E. H., Milton, D. C., Randall, S. L. W., Bui, L. D., Goldmann, N., Cameron, A., Laird, B., Talwar, D., Godber, I., Davidson, A., & Mcmillan, D. C. (2020). Prognostic factors in patients admitted to an urban teaching hospital with COVID-19 infection, *Journal of translational medicine*, 18 (354), 1-10.
- McNabb-Baltar, J., Jin, D. X., Grover, A. S., Redd, W. D., Zhou, J. C., Hathorn, K. E., Mccarty, T. R., Bazarbashi, A. N., Shen, L., & Chan, W. (2020). Lipase Elevation in Patients With COVID-19, *The American Journal of Gastroenterology*, 115 (8), 1286-1288.

- Nardo, A. D., Gleixner, M. S., Bakail, M., Dixon, E. D., Lax, S. F., & Trauner, M. (2020). Pathophysiological mechanisms of liver injury in COVID-19, *Liver International*, 41 (1), p. 20-32.
- Nogueira, S. A. R., Oliveira, S. C. S., Carvalho, A. F. M., Neves, J. M. C., Silva, L. S. V., Silva Junior, G. B., & Nobre, M. E. P. Renal changes and acute kidney injury in covid-19: a systematic review, *Revista da Associação Médica Brasileira*, 66 (2), 112-117.
- Paula, H. I., Amorim, D. L. A. N., Gonzaga, G. M., Batista, J. S., Ferreira, F. S. B., & Xavier, F. D. (2021) Alterações Hematológicas da Covid-19, *Brasília Médica*, 58, 1-6.
- Payen, D., Cravat, M., Maadadi, H., Didelot, C., Prosic, L., Dupuis, C., Losser, M. R., & Bittencourt, M. C. (2020). A Longitudinal Study of Immune Cells in Severe COVID-19 Patients, *Frontiers in Immunology*, 11, 1-12.
- Pereira, A. F., Terra, A. K. A., Oliveira, C. H. S., Terra, M. C., Oliveira, C. M., Carvalho, L. P., Oliveira, S. C., Rondono, K. O. L., Betelho, L. M., Oliveira, C. S., Camilo, F. F., Delmoro, A. C. L., & Salles, B. C. C. (2021). Alterações hematológicas e hemostasia na COVID-19: uma revisão de literatura. *Research, Society and Development*, 10 (11), 1-17.
- Pirsalehi, A., Baghestani, A., Sanadgol, G., Shirini, D., Baerz, M. M., Abdi, S., Akbari, M. E., & Bashash, D. (2021). Differential alteration trend of white blood cells (WBCs) and monocytes count in severe and non-severe COVID-19 patients within a 7-day follow-up, *Iranian Journal of Microbiology*, 13 (1), 8–16.
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., & Tian, D. S. (2020). Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China, *Clinical Infectious diseases*, 71, 762–8.
- Rother, E. T. (2007). Revisão sistemática X revisão narrativa. *Acta Paul Enferm.* 20 (2), 5-6.
- Saini, R. K., Saini, N., Ram, S., Soni, S. L., Suri, V., Malhotra, P., Kaur, J., Verma, I., Sharma, S., & Zohmangaihi, D. (2020). COVID-19 associated variations in liver function parameters: a retrospective study, *Postgraduate Medical Journal*, 98, 91-97.
- Santos, J. C. O., & Mendonça, M. A. O. (2015). Fatores predisponentes para lesão renal aguda em pacientes em estado crítico: revisão integrativa, *Revista da Sociedade Brasileira de Clínica Médica*, 13 (1), 69-74.
- Schulte-Schrepping, J., Reusch, N., Paclik, D., Babler, K., Schlickeiser, S., Zhang, B.; Kramer, B., Krammer, T.; Brumhard, S., Bonaguro, L., Domenico, E., Wendisch, D., Grasshoff, M., Kapellos, T. S., Beckstette, M., Pecht, T., Saglam, A., Dietrich, O., Mei, H. E., Schulz, A. R., Conrad, C. Kunkel, D., Vafadarnejad, E., Xu, C., Horne, A., Herbert, M., Drews, A., Thibeault, C., Pfeiffer, M., Hippenstiel, S., Hocke, A., Muller-Redetzky, H., Heim, K., Machleidt, F., Uhrig, A., Jarcy, L. B., Jurgens, L., Stegemann, M., Glosenkamp, C. R., Volk, H., Goffnet, C., Raabe, J., Kaiser, K. M., Vinh, M. T., Rieke, G., Meisel, C., Ulas, T., Becker, M., Geffers, R., Witzernath, M., Drosten, C., Suttorp, N., Kalle, C. V., Kurth, F., Handler, K., Schultze, J. L., Aschenbrenner, A. C., Li, Y., Nattermann, J., Sawitzki, B., Saliba, A., & Sander, E. (2020). Suppressive myeloid cells are a hallmark of 2 severe COVID-19, *MedRxiv*, <https://doi.org/10.1101/2020.06.03.20119818>
- Schulte-Schrepping, J., Reusch, N., Paclik, D., Babler, K., Schlickeiser, S., Zhang, B.; Kramer, B., Krammer, T.; Brumhard, S., Bonaguro, L., Domenico, E., Wendisch, D., Grasshoff, M., Kapellos, T. S., Beckstette, M., Pecht, T., Saglam, A., Dietrich, O., Mei, H. E., Schulz, A. R., Conrad, C. Kunkel, D., Vafadarnejad, E., Xu, C., Horne, A., Herbert, M., Drews, A., Thibeault, C., Pfeiffer, M., Hippenstiel, S., Hocke, A., Muller-Redetzky, H., Heim, K., Machleidt, F., Uhrig, A., Jarcy, L. B., Jurgens, L., Stegemann, M., Glosenkamp, C. R., Volk, H., Goffnet, C., Raabe, J., Kaiser, K. M., Vinh, M. T., Rieke, G., Meisel, C., Ulas, T., Becker, M., Geffers, R., Witzernath, M., Drosten, C., Suttorp, N., Kalle, C. V., Kurth, F., Handler, K., Schultze, J. L., Aschenbrenner, A. C., Li, Y., Nattermann, J., Sawitzki, B., Saliba, A., & Sander, E. (2020). Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment, *Cell*, 182 (6), p. 1419–1440.
- Shah, S. J., Barish, P. N., Prasad, P. A., Kistler, A., Neff, N., Kamm, J., Li, L. M., Chiu, C. Y., Babik, J. M., Fang, M. C., Abe-Jones, Y., Alipanah, N., Alvarez, F. N., Botvinnik, O. B., Castaneda, G., Dadasovich, R. M., Davis, J., Deng, X., Derisi, J. L., Detweiler, A. M., Federman, S., Haliburton, J., Hao, S., Kerkhoff, A. D., Kumar, G. R., Malcolm, K. B., Mann, S. A., Martinez, S., Mary, R. K., Mick, E., Mwakibete, L., Najafi, N., Peluso, M. J., Phelps, M., Pisco, A. O., Ratnasiri, K., Rubio, L. A., Sellas, A., Sherwood, K. D., Sheu, J., Spottiswoode, N., Tan, M., Yu, G., Kangelaris, K. N., & Langelier, C. (2020). Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: A retrospective cohort study of patients with and without COVID-19, *EClinicalMedicine*, 27 (100518), p. 1-17.
- Silvin, A., Chapuis, N., Dunsmore, G., Goubet, A. G., Dubuisson, A., Derosa, L., Almiro, C., Henon, C., Kosmider, O., Droin, N., Rameau, P., Catelain, C., Alfaro, A., Dussiau, C., Friedrich, C., Sourdeau, E., Marin, N., Szwebel, T., Cantin, D., Mouthon, L., Borderie, D., Deloger, M., Bredel, D., Mouthon, L., Borderie, D., Deloger, M., Bredel, D., Mouraud, S., Drubay, D., Adrieu, M., Lhonneur, A., Saada, V., Stoclin, A., Willekens, C., Pommeret, F., Griscelli, F., Ng, L. G., Zhang, Z., Bost, P., Amit, I., Barlesi, F., Marabelle, A., Pene, F., Gachot, B., Andre, F., Zitvogel, L., Ginhoux, F., Fontenay, M., & Solary, E. (2020). Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe From Mild COVID-19, *Cell*, 182 (6), 1401–1418.
- Su, H., Yang, M., Wan, C., Yi, L., Tang, F., Zhu, H., Yi, F., Yang, H., Fogo, A. B., Nie, X., & Zhang, C. (2020). Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, *Kidney International*, 98 (1), 219–227.
- Sun, S., Cai, X., Wang, H., He, G., Lin, Y., Lu, B., Chen, C., Pan, Y., & Hu, X. (2020). Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China, *Clinica Chimica Acta*, 507, p.174-180.
- Tajbakhsh, A., Gheibi Hayat, S. M., Taghizadeh, H., Akbari, A., Inabadi, M., Savardashtaki, A., Johnston, T. P., & Sahebkar, A. (2021). COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up, *Expert Review Of Anti-infect Therapy*, 19 (3), 345-357.
- Tan, Y., Zhou, J., Zhou, Q., Hu, L., & Long, Y. (2021). Role of eosinophils in the diagnosis and prognostic evaluation of COVID-19, *Journal Medical Virology*, 93 (2), 1105–1110.
- Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, *Journal of Thrombosis and Haemostasis*, 18 (4), 844–847.

- Verdoni, L., Mazza, A., Gervasoni, A., Martelli, L., Ruggeri, M., Ciuffreda, M., Bonanomu, E., & Dantiga, L. (2020). An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study, *Lancet*, 395 (10239), 1771-1778.
- Veira, L. M. F., Emery, E., & Andriolo, A. (2020). COVID-19: laboratory diagnosis for clinicians. An updating article, *São Paulo Medical Journal*, 138 (3), 259-266.
- Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020a). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China, *JAMA*, 323 (11), 1061–1069.
- Wang, F., Wang, J. N. H., Zhao, Q., Xiong, Y., Deng, L., Song, S., Ma, Z., Mo, P., & Zhang, Y. (2020b). Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia, *The Journal of Infectious Diseases*, 221 (11), 1762–1769.
- Westmeier, J., Paniskaki, K., Karaköse, Z., Werner, T., Sutter, K., Dölff, S., Overbeck, M., Limmer, A., Liu, J., Zheng, X., Brenner, T., Berger, M. M., Witzke, O., Trilling, M., Lu, M., Yang, D., Babel, N., Westhoff, T., Dittmer, U., & Zelinsky, G. (2020). Impaired Cytotoxic CD8+ T Cell Response in Elderly COVID-19 Patients, *mBio*, 11 (5), 1-13.
- World Health Organization. (2022). *Weekly epidemiological update on COVID-19 - 22 March 2022*. Geneva, World Health Organization, Edition 84
- Xavier, A. R., Silva, J. S., Almeida, J. P. C. L., Conceição, J. F. F., Lacerda, G. S., & Kanaan, S. (2020). COVID-19: manifestações clínicas e laboratoriais na infecção pelo novo coronavírus, *Jornal Brasileiro de Patologia e Medicina Laboratorial*, 56, 1-9.
- Ye, W., Chen, G., Li, X., Lan, X., Ji, C., Hou, M., Zhang, D., Zeng, G., Wang, Y., Xu, C., Lu, W., Cui, R., Cai, Y., Huang, H., & Yang, L. (2020). Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19, *Respiratory Research*, 21 (169), 1-7.
- Zancanaro, V., Moura, T. R., Bellaver, E. H., & Javorski, J. M. (2021). Alterações nos parâmetros hematológicos e imunológicos observadas na infecção pelo sars-cov-2: uma revisão sistemática de literature, *Brazilian Journal of Development*, 7 (5), 50745-50758.
- Zhang, J. J., Dong, X., Cao, Y. Y., Yuan, Y. D., Yang, Y. B., Yan, Y. Q., Akdis, C. A., & Gao, Y. D. (2020). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, *Allergy*, 75 (7), 1730-1741.
- Zhang, S., Liu, Y., Whang, X., Yang, L., Li, H., Whang, Y., Liu, M., Zhao, X., Xie, Y., Yang, Y., Zhang, S., Fan, Z., Dong, J., Yuan, Z., Ding, Z., Zhang, Y., & Hu, L. (2020). SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19, *Journal of Hematology and Oncology*, 3 (120), 1-22.
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult patients hospitalized with COVID-19 in Wuhan, China: a retrospective cohort study, *The Lancet*, 395 (10229), 1054-1062.
- Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., Sun, R., Tian, Z., Xu, X., & Wei, H. (2020). Pathogenic T-Cells and Inflammatory Monocytes Incite Inflammatory Storms in Severe COVID-19 Patients, *National Science Review*, 7 (6), 998–1002.
- Zhou, Z., Ren, L., Zhang, L., Zhong, J., Xiao, Y., Jia, Z., Guo, L., Yang, J., Wang, C., Jiang, S., Yang, D., Zhang, G., Li, H., Chen, F., Xu, Y., Chen, M., Gao, Z., Yang, J., Dong, J., Liu, B., Zhang, X., Wang, W., He, K., Jin, Q., Li, M., & Wang, J. (2020). Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients, *Cell Host Microbe*, 27 (6), 883-890.