

## PHYSIOPATOLOGICAL ASPECTS OF COVID-19 IN HUMANS

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### ABSTRACT

In December 2019, the largest epidemic associated with a Coronavirus began, SARS-CoV-2 (better known as COVID-19, or Coronavirus Disease / 2019). The first focus was in Hubei province, China, and since then it has spread throughout the world, reaching, until April 2020, almost 2.8 million people and approximately 193 thousand deaths worldwide. The agent causes respiratory, hemodynamic, digestive and inflammatory disorders, which can lead to death in any individual, although the lethality rate is higher in individuals over 60 years and with some comorbidity, such as diabetes or previous cardiac problems. The present study describes the pathogenesis of the agent and the anatomopathological lesions induced by COVID-19 in humans.

**Keywords:** coronavirus, pneumonia, viremia, inflammation, one health

### INTRODUCTION

The spread of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) began in December 2019. The largest epidemic associated with a Coronavirus described (COVID-19 - Coronavirus Disease / 2019). The first focus occurred in Hubei province, China. Since then it has spread throughout the world, reaching almost 2.8 million people and approximately 193 thousand deaths worldwide until April 2020 (WHO, 2020; PINTO et al., 2020).

The pathogenesis of COVID-19 in humans is not fully known. Some patients manifest moderate symptoms of the disease. Others have more pronounced signs and die due to multiple complications in different organs (LIN et al., 2020).

Among the coronaviruses that can cause disease in humans, three are more important. In addition to SARS-CoV-2, there is SARS-CoV - discovered in 2002, responsible for severe acute respiratory syndrome; and Mers-CoV - discovered in 2012, which caused the Middle East respiratory syndrome (ZHENG, 2020).

This study aimed to analyze the types of cell lesions and the mechanism by which the coronavirus acts in the cells.

## DEVELOPMENT

Coronavirus, belongs to the family *Coronaviridae*, subfamily *Orthocoronaviridae*, divided into the genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. In the genus *Alphacoronavirus*, the Canine Coronavirus (Enteric) and the Feline Coronavirus (Feline Infectious Peritonitis) has been described (JAIMES et al., 2020).

The *Betacoronavirus* Genus describes the agents of Severe Acute Respiratory Syndrome caused by Coronavirus - SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus); Middle East Respiratory Syndrome caused by Coronavirus- MERS-CoV (the Middle East Respiratory Syndrome Coronavirus) and more recently, SARS-CoV-2, or better known as COVID-19 (Coronavirus Disease 2019). *Betacoronaviruses* also have other viruses that affect humans, bats, and animals and, while MERS-CoV has a relatively stable genome, the other components of this genus have a high rate of mutation and recombination. (JAIMES et al., 2020). Thus, there is some evidence to guide the origin of COVID-19 in the recombination of a Bat Coronavirus. For contamination of humans to happen, recombination is usually necessary, with the passage of the virus in another animal species. In the case of COVID-19, the great suspicion is that this passage occurred in Pangolin (*Manis javanica*), but the participation of other animal species, such as snakes and birds, is not ruled out (LUAN et al., 2020; JAIMES et al., 2020; HUYNH et al., 2012).

Most patients who died of COVID-19 had comorbidities such as hypertension, diabetes, and chronic obstructive pulmonary disease. Comparing these individuals with those who do not have these diseases, there is an increase in the activity of the gene responsible for the production of Angiotensin-Converting Enzyme 2 (ACE2), identified as a facilitating factor for the entry of the virus into cells (PINTO et al., 2020). Among the target cells, are described type II alveolar cells, myocardial cells, ileum, kidney, and esophagus, as well as bladder epithelial cells (LUAN et al., 2020; JAIMES et al., 2020; HUYNH et al., 2012). Since this ACE2 receptor is functionally similar among mammals, COVID-19's ability to infect other species is inferred, although this fact has not yet been definitively proven (LUAN et al., 2020).

Two interrelated processes occur, the cytopathic effect of the virus on the host cells at an earlier stage, and a later exacerbated inflammatory response. Phenotypically, these two processes are responsible for three distinct stages – correlated to the symptoms, clinical findings, and response to treatment. It is important to establish that not all patients necessarily go through these stages. In the first stage, the direct action of viruses on cells occurs, triggering mild clinical signs, such as cough, fever, asthenia, headache, myalgia, lymphopenia, and neutrophilia; in the second stage, or pulmonary phase, there is a decrease in viremia and an increase in the inflammatory cascade, causing tissue damage and dyspnea, as well as worsening lymphopenia and elevated transaminases, with or without associated hypoxia; in the third stage is the hyperinflammatory phase, with severe systemic manifestations and worsening of the pulmonary condition (SIDDIQI and MEHRA, 2020).

The hyperinflammatory phase, also known as Cytokine Release Syndrome (CRS) or Cytokine Storm may be related to hemophagocytic syndromes, or hemophagocytic lymphohistiocytosis (HLH), which occur when NK (natural killer) cells and cytotoxic T lymphocytes do not eliminate activated macrophages, thereby increasing the production of pro-inflammatory cytokines (MEHTA et al., 2020). This syndrome is not exclusive to COVID-19, as it has already been described in other types of viral, bacterial or even infections caused by toxins and can cause vascular fragility, tissue toxicity, edema, shock in the host, culminating in multiple organ failure (ZHOU et al., 2020). In adults, HLH commonly triggered by viral diseases and occurs in 3.7 to 4.3% of cases of sepsis (JANKA and LEHMBERG, 2014).

MEHTA et al. (2020) reported that some patients presenting the disease most severe clinical condition suffer from a “cytokine storm” or hypercytokininaemia, which activates a lymphohistiocytosis hemophagocytic, which is one of the important factors of mortality in humans. The main cytokines identified in these patients were: interleukins (IL) 2 and 7; granulocyte colony-stimulating factor; protein 10 inducible by interferon- $\gamma$ ; monocyte-chemotactic protein 1; inflammatory macrophage protein 1- $\alpha$ ; and tumor necrosis factor- $\alpha$ . The authors argue that laboratory changes observed in HLH should be tracked to know the COVID-19 phenotype. The cardinal signs of HLH include persistent fever, hyperferritinemia, and in 50% of cases, respiratory involvement, such as the Acute Respiratory Discomfort Syndrome (ARDS), the main cause of death in humans. In severe cases, a significant reduction in T lymphocytes (mainly CD8 +) was observed, in addition to the addition of IL-6, IL-10, IL-2, and IFN- $\mu$  in peripheral blood. After the patients' recovery, the levels returned to their normal values (ZHOU et al., 2020).

The COVID-19 can also predispose the patient to the formation of thrombi, arterial and venous, due to the excessive inflammatory process, platelet activation, endothelial dysfunction, and blood stasis triggering in some cases the disseminated intravascular coagulation, with serious systemic implications (BIKDELI et al., 2020). The Centers for Disease Control and Prevention (CDC), based on information about COVID-19, has initiated a post mortem collection guide and shipment of material from cadavers suspected of having the disease or with a confirmed diagnosis. The autopsy must be performed in laboratories with the isolation of airborne agents, which does not exist in Brazil (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2020). In the lungs of two patients who underwent pulmonary lobectomy due to the presence of adenocarcinoma, and later confirmed to have SARS-CoV-2, some microscopic changes were observed, such as edema, protein exudate, pneumocyte hyperplasia, irregular inflammatory infiltrate and giant multinucleated cells. None of the patients showed signs of pneumonia until the date of the surgery, meaning that these are microscopic findings from the early stages of COVID-19. These are important findings, as autopsies have not been performed on victims of this disease, due to the safety of the medical team (TIAN et al., 2020).

In Brazil, preliminary studies of the post-mortem examinations in individuals who died of COVID-19 have been carried out and confirmed severe lung injuries. These tests performed using computed tomography and ultrasound images to guide the needle puncture of some organs (lungs, kidneys, liver, spleen, and heart). There was no opening of the cadaver in these cases to keep the safety of the team that performed the procedure. The tissue samples showed intense epithelial desquamation of alveoli, chronic kidney, heart damage due to hypertension and cardiac ischemia, liver damage associated with diabetes, and acute sepsis damage (ZORZETTO, 2020).

## CONCLUSION

SARS-CoV-2 is an emerging virus, and the main reactions exhibited by the patient are related to aggravated inflammation and hypercoagulability, leading to the death of some individuals, due to acute systemic insufficiency. A better understanding of this pathogenesis and its mechanisms related to the exacerbated immune response, which is a major cause of death, will make it possible to try to adopt therapeutic measures capable of modulating this immune response and thus mitigating the effects in the patient, increasing the success rate of treatment.

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