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REVIEW

The first year of the covid-19 pandemic: what is known about its physiopathological constructs

Primeiro ano de pandemia COVID-19: o que se sabe sobre seus constructos fisiopatológicos

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ABSTRACT

COVID-19 is caused by the SARS-CoV-2 virus, which has triggered an emerging public health situation, decimating millions of people and leaving other social problems. This study aimed to present the pathophysiological constructs in the first year of the pandemic. This is a narrative review of the literature, based on searches in the Virtual Health Library, Capes Periodicals, PubMed, and Cochrane databases with the standardized descriptors 'Pathophysiology' combined using the Boolean AND operator. Articles published in the first year of the pandemic in any language dealing with this topic were selected. This review found that COVID-19 has three pathophysiological phases: inoculation; pneumonia; and systemic hyperinflammation. Each phase defines the clinical manifestations and evolution of the disease, as well as the tests to be performed. Despite numerous studies, there are still gaps such as the rapid evolution of the infection and the definitions of the pathophysiological processes and the sequelae of this morbidity.

RESUMO

A COVID-19 é causada pelo vírus SARS-CoV-2, que provocou uma situação emergente de saúde pública, dizimando milhões de pessoas e deixando outros problemas sociais. Esse estudo teve por objetivo apresentar os construtos fisiopatológicos no primeiro ano da pandemia. Trata-se de uma revisão narrativa da literatura, realizada a partir de pesquisas nas bases Biblioteca Virtual de Saúde, Periódicos Capes, PubMed, Cochrane com os descritores padronizados '*Pathophysiology*' combinados por meio do operador booleano AND. Selecionaram-se artigos publicados no primeiro ano da pandemia de qualquer idioma e que tratassem desse tema. Os resultados dessa revisão constataram que a COVID-19 possuí três fases fisiopatológicas: inoculação; pneumonia; e hiperinflamação sistêmica. Cada fase define as manifestações clínicas e a evolução da doença, bem como, os exames a serem realizados. Apesar de inúmeros estudos, ainda há lacunas como a evolução rápida da infecção e as definições dos processos fisiopatológico e as sequelas dessa morbidade.

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Introduction

COVID-19 is caused by the SARS-CoV-2 virus. It was first identified in the city of Wuhan in China in 2019 on December 8, 2019[1]. On January 30, 2020, the World Health Organization (WHO) declared the Coronavirus outbreak as a Public Health Emergency of International Concern, and on March 11, it declared a state pandemic, with 110,000 cases and 4,000 deaths spread across all continents[2]. SARS-CoV-2 is a zoonotic virus in the coronavirus family that causes acute respiratory distress syndrome. The magnitude of contamination by the disease is due to the potential for transmission by droplets among infected people[3].

Exactly one year after the declaration of the pandemic by the WHO, a historic milestone of the health crisis in the modern world, on March 11, 2021, 117.799,584 million confirmed cases were registered globally, including 2.615,018 deaths reported to the WHO. Until these data, vaccines, as the main measure to combat the pandemic, had been treated in a total of 300,002,228 doses[3].

Amidst humanity's greatest pandemic of the last century, COVID-19 has already claimed over 3 million lives in just over a year since the first cases[3]. The pandemic has caused social and health problems, becoming a global crisis that transcends anthropogenic, natural, biological, and geopolitical aspects. Despite following preventive measures, any pandemic disrupts social, cultural, and economic relations, as well as families, education, and people's health[4].

In this crisis scenario, it becomes crucial to approach accurate and relevant information about the pathophysiological constructs and clinical consequences of this disease, as there is an infodemic[5], and stopping misinformation is paramount for effective communication[6].

Answering questions about COVID-19 aligns with the main research priorities outlined in the Global Research Roadmap by the World Health Organization. These priorities include the natural history of the virus, epidemiology, diagnosis, clinical management, ethical considerations, social sciences, as well as long-term goals for therapeutics and vaccines[7].

In this perspective, this study aims to present the pathophysiological constructs of SARS-CoV-2 regarding transmission and dissemination, innate and adaptive immune processes, clinical manifestations, and diagnostic methods, based on scientific studies published in the first year of the COVID-19 pandemic.

Methods

This is a narrative study of materials published between March 11, 2020, and March 10, 2021, sourced from Cochrane, Capes Journals, PubMed, and the Virtual Health Library. Narrative reviews are comprehensive publications in which the materials are analyzed in a generalized manner and incorporated to address the proposed objectives[8].

The importance of using a narrative review for the problem this study aims to address is due to the fact that COVID-19 is a new/emerging disease, and all published material about it thus far is of utmost relevance to be considered. Other types of reviews would not be able to encompass all aspects and sources of information that contribute to understanding the pandemic. Therefore, this narrative review, to build the 'state of the art' of COVID-19 in its first year of the pandemic, consolidated various sources of information, including materials published in scientific journal databases, as well as governmental and health guideline-setting institutions such as WHO and OPAS.

To compose this review, the search for publications was conducted using the following English-language descriptors/terms: Pathophysiology AND COVID-19. Considering that COVID-19 is a new/emerging disease, all published and validated material about it at this moment is relevant to be considered for a narrative. However, the following inclusion criteria were applied: materials in English, Spanish, and Portuguese, peer-reviewed and published in the following formats: articles, case reports, editorials. Additionally, documents, technical notes, and epidemiological bulletins were included. All titles and abstracts of the identified studies were read and analyzed by two authors to adopt eligibility criteria. The full texts of the included studies were reviewed by a single author.

A total of 181 studies were identified, with 44 duplicates and 137 selected. Out of these, 68 manuscripts were excluded as they did not substantially meet the purposes of this review. After considering the exclusion and inclusion criteria, 69 studies were selected to compose this narrative, as shown in **Figure 1**.

Results and Discussion

The following section presents the results and discussion of studies published by authors on transmission, immune responses, pathogenicity, and clinical manifestations of COVID-19 in its first year of the pandemic. The material derived from this review is presented in a narrative, impersonal, and unbiased manner.

The results of the identification and selection of articles related to the pathophysiological constructs are appropriately categorized by themes, references, and summaries as shown in **Table 1**.

Transmission and dissemination of SARS-CoV-2

The first phase of disease spread occurred in December 2019 with a localized outbreak in Wuhan, China, due to exposure at the Huanan Seafood Wholesale Market, where various species of wild animals are traded[9]. This phase lasted until January 13, 2020, when cases outside of Wuhan emerged, indicating direct person-to-person transmission. Prior to January 13, on January 7, patients with the disease were identified who had not visited the food wholesale market more than 14 days before the onset of symptoms[10].

The transmission process became clear on January 21, 2020, when the WHO tweeted that the contamination among healthcare professionals made it evident that transmission occurs from person to person. As a result, the WHO published the first technical guidance on home care for patients with suspected infection[11].

Person-to-person transmission occurs through three main routes: (1) respiratory droplets from person to person in indoor settings, (2) between individuals and the contaminated environment through contact with circulating aerosols in the air, and (3) between individuals and contact with contaminated surfaces[12, 13].

The review studies have indicated that SARS-CoV-2 can remain active on various surfaces for different durations: aerosol form for 3 hours, copper for 4 hours, paper for 24 hours, and plastic and stainless steel for three days[12].

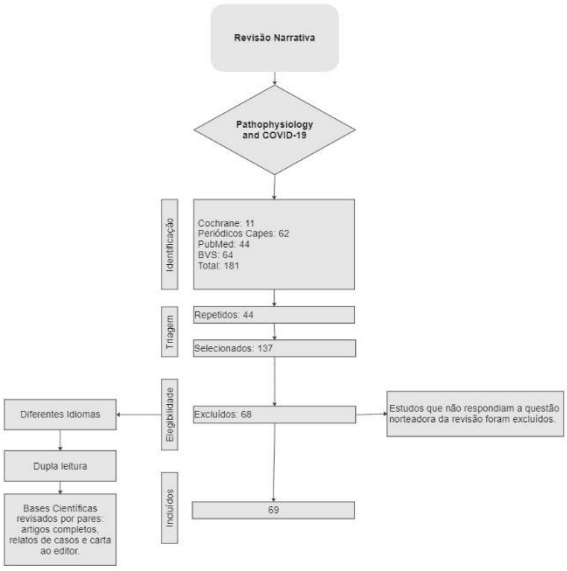

Figure 1. Flowchart/Prisma for article identification and selection. Chapecó, SC, Brazil (2021). **Source:** authors.

Studies have indicated that the incubation period of COVID-19 ranges from two to 14 days, but it can extend up to 27 days[14]. The average time from exposure to symptom onset is around five days, and 97.5% of individuals develop symptoms within 11.5 days[13]. COVID-19 is a highly transmissible, silent, and pathogenic viral infection that can lead to Severe Acute Respiratory Syndrome[15].

Table 1. Results of the identification and selection of articles regarding the themes, references, and synthesis of the material found in the first year of the COVID-19 pandemic, 2021.

Theme	References		Synthesis
Transmission and Dissemination of SARS-CoV-2	BHAT et al. CARVAJAL; PARRA; SILANO, GUO et al. SHEREEN et al.	GONZÁLEZ G. LI et al. PENG et al. SEPÚLVEDA C.; WAISSBLUTH A.;	The transmission of COVID-19 occurs primarily through person-to-person contact, specifically through close contact with respiratory droplets carrying the SARS-CoV-2 virus.
Immune Response	PARRA-IZQUIERDO; FLOREZ-SARMIENTO; ROMERO-SANCHEZ. YUKI; FUJIOGI; KOUTSOGIANNAKI. ZHAO et al.	BASTARD et al. CARVAJAL; PARRA; SILANO, MARKET et al. SINGH et al.	The immune system responds to the identification of antigens, including those from SARS-CoV-2, through both natural and adaptive immune responses.
Pathogenicity	CARVAJAL; PARRA; SILANO. DHOCHAK et al, GATTIONI et al. PÉREZ A; CORDERO R; AVENDAÑO C. STEARDO et al., (2020) XIAO; SAKAGAMI; MIWA. YUKI; FUJIOGI; KOUTSOGIANNAKI.	JAIN; DOYLE. KASAL; LORENZO; TIBIRIÇÁ. MEFTAHI et al. ROCHA., GENGLER et al. YLIKOSKI; MARKKANEN; MÄKITIE.	Addressed the pathological processes caused by COVID-19, in the respiratory, gastrointestinal, cardiac, hematological, renal and neural, and sensory systems. It showed the systemic and multiple organic changes resulting from the SARS-CoV-2 infection and the parallel action of the immune system.
Clinical manifestations	ABOU-ISMAIL et al., ASGHARPOUR et al., CARVAJAL; PARRA; SILANO. NG et al., PETROVIC et al., PIAZZA; MARROW. PIERINI et al. SEPÚLVEDA C.; WAISSBLUTH A.; GONZÁLEZ G. SHRESTHA et al., SINGH et al., TU et al., YLIKOSKI; MARKKANEN; MÄKITIE, YU; SUN; FENG.	AHMADIAN et al., DAS., ABBOUD et al., TSATSAKIS et al., SIRIPANTHONG et al., RODRIGUEZ-MORALES et al., LIU et al., LIU et al., (2020b) TERCEIRO; VIETTO. POOR et al., VIOLETIS et al., BARROS et al., GRASSELLI et al., SABIONI et al., STEARDO et al., WIERSINGA et al. YUKI; FUJIOGI; KOUTSOGIANNAKI.	It highlights the main clinical manifestations resulting from the COVID-19 infection, such as signs and symptoms, in the different forms of the severity of the disease.
Diagnosis	CARVAJAL; PARRA; SILANO; SINGH et al., CORMAN et al. GONZÁLEZ G., SEPÚLVEDA C.; WAISSBLUTH A.;	DAS; LEVETT et al., LIU et al. PARASHER; RAFIEE et al., SINGH et al.,	It consists of demonstrating the imaging, immunoenzymatic, immunoassays, and laboratory tests performed to diagnose the disease COVID-19.

Source: authors.

Innate and Adaptive Immune Response

The first immune response to be activated is the innate response, where the body's defense cells identify antigens (viruses) or foreign bodies, in this case, SARS-CoV-2. There are three types of defense cells involved: epithelial cells, alveolar macrophages, and dendritic cells[12].

After the innate response, the adaptive immune response begins with the activation of T cells (CD4+ and CD8+ T lymphocytes) by dendritic cells and macrophages. CD4+ cells activate B cells to produce specific antibodies that can neutralize the infecting virus[16]. CD8+ cells induce apoptosis in infected cells, effectively eliminating them.

The antibodies produced by CD4+ cells are proteins called immunoglobulins, which recognize and eliminate other virus-infected cells. If the adaptive response is strong enough, it can prevent the progression to severe disease or reinfection by the same virus[17].

The massive and prolonged recruitment of defense cells to the lungs during infection has led to laboratory findings of lymphopenia (reduced lymphocyte count) and high concentrations of pro-inflammatory mediators such as interleukins (IL-6, IL-10) and colony-stimulating factors like granulocyte and monocyte inflammatory proteins and tumor necrosis factor[18].

In a study, it was notably found that 95 out of 101 patients with severe forms of the disease developed neutralizing autoantibodies against type I interferons (IFNs). The hypothesis is that the neutralization of autoantibodies against type I IFNs may be the basis for the severity of COVID-19 by impairing the binding of type I IFNs to their receptor and the downstream responsive pathway (BASTARD et al., 2020). The reduction in the number of circulating natural killer (NK) cells and an exhausted phenotype after SARS-CoV-2 infection may be a predictive marker for disease progression and severity of COVID-19[19].

The results indicate a dual function of NK cells during coronavirus pathogenesis. The first function suggests that NK cells in healthy individuals with low risk can recognize SARS-CoV-2-infected cells through viral proteins on the surface of infected cells and by detecting cytokines and chemokines produced in response to infection. These cells are hypothesized to induce apoptosis by releasing

cytotoxic granules.

The second function involves individuals at high risk, where dysfunctional NK cells may fail to recognize and respond to SARS-CoV-2 infection due to immune evasion strategies employed by the virus. It is hypothesized that an accumulation of infected epithelial cells and innate immune cells, such as monocytes-macrophages and neutrophils, release cytokines and chemokines that recruit immune cells, including NK cells, to the lungs. This can result in the induction of a cytokine storm, led by IFN-γ[19].

Pathogenicity of COVID-19

COVID-19 exhibits three physiopathological phases: inoculation, infection of the lower respiratory system, and the third phase of systemic hyperinflammation. The reasoning can be summarized as follows: I - Onset of Hypoxia; II - Endothelial Dysfunction; III - Pulmonary Manifestations of the disease[20]. These authors challenge the classification of COVID-19 pneumonia stages based on the editorial by Gattioni et al. (2020), which categorizes phenotypes as 'L-type' and 'H-type'. The 'L-type' corresponds to Stages 2 and 3 of pneumonia. However, the study by Pérez, Cordero, and Avendaño, along with other authors, approach the pathophysiological stages in three phases[21]:

Stage I - Inoculation Phase (attachment, inoculation, replication, maturation, and transmission of SARS-CoV-2). The spike proteins of SARS-CoV-2 interact with ACE2, undergoing cleavage by TMPRSS2, allowing the virus to enter the cell. However, when ACE2 is cleaved by the protease ADAM17, SARS-CoV-2 is unable to enter the cell, thus protecting it. Dysfunction of ACE2 caused by SARS-CoV-2 infection can worsen the severity of the disease[22].

According to the authors Yuki, Fujiogi, and Koutsongiannaki (2020), the virus's life cycle in the host consists of five stages: attachment, penetration, biosynthesis, maturation, and release. Attachment and penetration occur in the nasosinusal region on epithelial cells, involving the interaction between the virus and ACE2 receptors. SARS-CoV-2 negatively regulates ACE2 in type II alveolar epithelial cells[20].

Upon entry into host cells through endocytosis or membrane fusion, the viral mRNA initiates biosynthesis, leading to the production of new viral particles. Subsequently, the process of maturation and release of the virus into the extracellular environment begins, marking the transmission phase, which still occurs in the nasosinusal region[12; 21; 23.]

Most patients are able to contain the infection at this point through their immune system. However, other patients develop severe forms of the disease, characterized by an intense and exacerbated immune response that compromises various organ functions[21].

Stage II: This refers to the stage in which there is infectious involvement of the lower respiratory system in both lungs. The SARS-CoV-2 virus triggers a systemic inflammatory response, leading to the production of exudate, a mixture of fibromyxoid material, hyaline membrane particles, and interstitial inflammatory infiltrates rich in lymphocytes. Atypical multinucleated cells indicating viral cytopathic changes are found in the alveolar spaces. This stage leads to the clinical condition of pneumonia, which impairs respiratory ventilation and requires hospitalization[21].

Stage III: In a minority of patients, a systemic hyperinflammation occurs, which represents the most critical stage of the disease as it behaves extrapulmonarily, affecting other organs. This stage can be divided into two phases.

The first phase (IIIa) is characterized by a primary inflammatory response. It can be attributed to three main causes. The first and most likely cause is rapid and accelerated viral replication, leading to apoptosis of epithelial cells, increased vascular permeability, and the release of pro-inflammatory cytokines and chemokines, leading to the recruitment of inflammatory infiltrates. This explains the peripheral leukopenia. The second probable cause is the dysregulation of the ACE2 membrane protein, which leads to rapid inflammation by increasing vascular permeability, resulting in edema and subsequent organ dysfunction[24,21,22]. Excessive inflammation plays a crucial role in the pathogenesis of the disease and can be debilitating, including septic shock[25]. The third cause is attributed to the antiviral response, where the immune system induces apoptosis due to increased pro-inflammatory responses.

The second phase (IIIb) involves the generalized adaptive immune response and the emergence of neutralizing antibodies, which can cause persistent lung damage and increase the risk of death. It is presumed that anti-S IgG alters the polarity of macrophages by inhibiting the interaction between the macrophage Fc receptor and anti-S IgG bound to the virus. The result of this interaction is a decrease in the production of pro-inflammatory cytokines and/or activation of the classical pathway of the complement system, leading to increased cellular damage. It is believed that the dysregulation of the inflammatory response causes an excessive release of cytokines and chemokines, resulting in a generalized syndrome and multiorgan dysfunction followed by death[21].

Another scientific observation is the negative regulation of ACE2 in pulmonary epithelium. Without the counteracting effects of ACE1, pulmonary capillary endothelial cells are unprotected, reducing the protective activity of ACE2-Ang-1-7-Mas-R while increasing the harmful activity of ACE1-Ang-II-AT1-R. The early deleterious effect of ACE1-Ang-II-AT1-R hyperactivity is possibly the release of a potent vasoconstrictor such as endothelin-1 from the pulmonary endothelium. ACE2-Ang-1-7-Mas-R inhibits the release of nitric oxide in the pulmonary endothelium. The development of severe pulmonary vasoconstriction leads to angiogenesis and an increase in the veno-arterial shunt fraction, resulting in severe hypoxia. The progression of alveolar-capillary barrier disruption causes proteins, fibrin, cells, and fluid to leak into the alveolar space, resulting in patchy ground-

glass opacities in both lungs as identified by computed tomography[20].

The "endothelial-epithelial" interaction plays a crucial role in the progression of the disease. After the rupture of the alveolar-capillary membrane, SARS-CoV-2 enters the pulmonary capillaries and triggers an activated inflammatory and coagulation process. This accelerates the induction of alveolar epithelial and endothelial cells and orchestrates the cytokine storm[20].

The endothelium plays a fundamental role in the organ dysfunction associated with severe infection and subsequent sepsis. The evidence regarding the pathophysiology aligns when considering the various complications of COVID-19, such as microvascular dysfunction, with an emphasis on the renin-angiotensin system[26].

The review provided insight into the pathophysiology in children. The most discussed hypotheses indicate a decrease in ACE2 receptors in children, as well as a less evolved innate immune inflammatory response. This reduces the likelihood of hyperinflammation[21, 27, 28].

In the case of elderly individuals who are susceptible to immunosuppression and have a lower capacity for regeneration of alveolar epithelium due to senescence and other exposures, they are a vulnerable risk group for contracting COVID-19 infection and subsequently experiencing death[27]. The elderly may also have a predisposition to produce more pro-inflammatory cytokines[24].

Clinical manifestations

The authors Yuki, Fujiogi e Koutsongiannaki (2020) proposed a classification of COVID-19 symptoms as outlined in **Table 2**.

Table 2. Classification of symptoms and clinical manifestations of COVID-19, 2021.

Classification/Clinical Status	Symptoms/Clinical Manifestations
Asymptomatic	Positive test for COVID-19 and normal chest imaging. No symptoms or clinical signs present.
Mild	Symptoms such as fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing, or digestive symptoms like nausea, vomiting, abdominal pain, and diarrhea.
Moderate	Pneumonia (frequent fever, cough) without evident hypoxemia, chest computed tomography showing lesions.
Strong	Pneumonia with hypoxemia (SpO2 <92%).
Critical	Acute Respiratory Distress Syndrome (ARDS) may be accompanied by shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction, and acute kidney injury.

Source: authors.

The most common symptoms of COVID-19 include fever, dry cough, shortness of breath, fatigue, muscle pain, and headache [12; 13; 29; 30; 31; 32]. In a smaller estimate, up to 13% of infected individuals develop severe forms of the disease, which can lead to pneumonia, shock, respiratory failure, and multiorgan failure followed by death[31; 33]. The extrapulmonary symptoms of COVID-19 may be associated with dominance of the sympathetic autonomic system (reduced parasympathetic function) as the central nervous system can be strongly activated by the neuroimmune axis in response to an inflammatory reflex due to inadequate immune defense[25].

During severe COVID-19 infection, clinical manifestations can occur in multiple organs. This represents a responsive way for the body to control the viral infection. Infection with SARS-CoV-2 can impair pulmonary, hematological, cardiovascular, renal, gastrointestinal, neurological, sensory, cutaneous, and immune susceptibility functions[34].

Pulmonary clinical manifestations

The clinical pulmonary manifestations of COVID-19 initially resemble those of a common flu. It starts with throat irritation and progresses to a dry cough and dyspnea. In a systematic review of 43 studies involving 3,600 patients, 60.3% reported cough[32], 45.6% reported dyspnea[31], and 23.5% reported sore throa.

Severely ill COVID-19 patients have preserved lung mechanics despite significant abnormalities in gas exchange, which is more consistent with pulmonary vascular disease[35; 36]. According to studies, 32.8% to 41.8% of patients progress to acute respiratory distress syndrome (ARDS)[31; 33].

Hematological clinical manifestations

The hematological clinical manifestations in severe COVID-19 infection involve thrombotic events, as evidenced by laboratory abnormalities such as lymphopenia, neutrophilia, prolonged prothrombin time, and elevated D-dimer levels[12; 37]. Laboratory findings, including lymphocyte count, creatinine levels, platelet volume in relation to lymphocytes, and lymphocyte-to-monocyte ratio, have been identified as independent prognostic factors for COVID-19[37, 38].

Many patients with severe COVID-19 have demonstrated abnormal blood coagulation, with increased levels of D-dimer and higher rates of venous thromboembolism[35, 36]. Consistently, elevated levels of D-dimer have emerged as an independent risk factor for poor outcomes, including death[39].

A study conducted in Italy with 301 COVID-19 patients, published in The Lancet in December 2020, found that 297 patients with severe disease showed greater adhesions than 95% of the classical cohort, and 94% of these patients had high levels of D-dimer concentration, consistent with hypoperfusion in both lungs, indicating a clinical consequence of thromboembolism[40].

COVID-19 can predispose individuals to venous and arterial thromboembolic diseases due to excessive inflammation, hypoxia, immobilization, and disseminated intravascular coagulation[41, 18], which are common in critically ill COVID-19 patients[42]. The coagulopathies are a

result of systemic vascular damage directly caused by the virus in the endothelium, leading to a thrombotic state and contributing to the high mortality rate[43].

Cardiovascular clinical manifestations

COVID-19 can lead to cardiac dysfunction and myocarditis. The progression of COVID-19 pathophysiology related to myocarditis involves cardiac injury and damage caused by the host's exacerbated immune response[12, 33]. Clinical findings include changes in electrocardiogram readings and impaired cardiac biomarkers. Many COVID-19 patients have pre-existing cardiovascular comorbidities and can experience myocardial infarction. Arrhythmias are not uncommon in COVID-19 patients, although the exact pathophysiology is still speculative. However, physicians should remain vigilant in providing immediate monitoring and treatment[36, 44, 45].

Microvascular damage occurs due to high serum concentrations of pro-inflammatory cytokines and chemokines in patients with COVID-19 compared to a control group[46].

Renal clinical manifestations

Renal involvement in COVID-19 typically occurs in patients who develop acute respiratory distress syndrome or multiorgan failure. Renal damage in COVID-19 has been shown to be multifactorial, involving direct viral infection, indirect injury from sepsis, hemodynamic changes, cytokine storm, and disseminated intravascular coagulation[33, 47].

SARS-CoV-2 can cause kidney damage, and based on the ACE2 pathway, it can lead to acute tubular necrosis. Dysregulation of immune responses induced by SARS-CoV-2, including cytokine storm, macrophage activation syndrome, lymphopenia, endothelial dysfunction, hypercoagulability, rhabdomyolysis, and sepsis, may be other causes of acute kidney injury. Additionally, hypoxia and low tissue oxygen perfusion in the kidney can result in ischemic injury[48, 49].

Gastrointestinal clinical manifestations

In a systematic review that included 60 articles and 4,243 patients with gastrointestinal symptoms such as nausea, vomiting, and diarrhea, it was found that the presence of these symptoms was associated with a higher severity of fever, acute respiratory distress, liver injury, and shock compared to those without gastrointestinal symptoms. Diarrhea, chest discomfort, and nausea/vomiting were less commonly reported symptoms in this group[32].

Neurological clinical manifestations

The SARS-CoV-2 virus is neurotropic, like other coronaviruses, and can enter the central nervous system through intranasal inoculation and peripheral nerves and synapses. It infects neurons and neuroglial cells in the brainstem through endocytosis, utilizing the ACE2 membrane protein. Neurons in the brainstem are directly involved in cardiorespiratory control, and lesions in these areas can exacerbate respiratory failure. In addition, hypoxia and the virus's neurotropic properties can lead to the development of acute and chronic neuropsychiatric and cognitive impairments[50].

Neurological disorders associated with COVID-19 can manifest in various ways, ranging from mild and nonspecific symptoms such as headache, muscle pain, and hyposmia, to more severe conditions including cerebrovascular disease and intracranial infections. Severe neurological symptoms, such as acute cerebrovascular disease, occur in only a minority of patients with usual risk factors and are associated with poor outcomes. However, the majority of COVID-19 patients exhibit only mild or minor neurological symptoms[51, 52].

Sensory clinical manifestations

In South Korea, approximately 30% of COVID-19 patients experienced hyposmia/anosmia, while in Germany, the prevalence was above 65% in people infected with the virus. Similar findings have been observed in other countries as well. It has been noted that the occurrence of hyposmia/anosmia is higher in patients under the age of 40[33].

The clinical manifestations of hyposmia/anosmia may be related to deficiencies in the autonomic reflexes of the cardiovascular system. This is because the SARS-CoV-2 virus interacts with ACE2 in neurons of the brainstem and central nervous system, leading to neuroinflammation and impairing organ functions[50]. Another study, in a systematic review, reported clinical findings associated with the virus, such as anosmia and neuroepithelial alterations or blockage of chemical receptors in sensory cells[33].

Cutaneous clinical manifestations

A study conducted in Spain with 375 cases investigated five skin infection pathologies, including maculopapular rashes associated with hospitalization. The study identified maculopapular rashes (47%), urticarial lesions (19%), areas of vesicles (19%), other vesicular eruptions (9%), and skin lesions and necrosis (6%) as cutaneous manifestations of COVID-19[32].

Infectious clinical manifestations

Patients with COVID-19 present a clinical picture of immune suppression and are prone to developing other infections, as hospitalization exposes them to invasive procedures, increasing the risk of infection with more susceptible bacteria such as *Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumoniae*[33].

Diagnosis of COVID-19

It involves imaging exams, immunoenzymatic and immunoassay tests, and biochemical tests. Imaging exams include radiography, magnetic resonance imaging (MRI), and computed tomography (CT) scans. Simple radiography is the most sensitive method to detect

pulmonary changes, and CT scans are an auxiliary method that can confirm COVID-19-related lung problems[12]. Chest CT images are highly sensitive and specific[53].

The most common findings in CT scans include bilateral ground-glass opacities in 39 cases (75%), consolidation in 18 cases (34.6%), and interlobular thickening in 4 cases (7.6%). Additionally, mediastinal lymph node involvement was observed in 14 cases (27%) and hilar lymph node involvement in 10 cases (19.2%)[54].

Immunoenzymatic and specific molecular diagnostic tests have been recommended to detect the viral protein of COVID-19. Reverse transcription polymerase chain reaction (RT-PCR) tests should be performed during the first week of symptom onset, and in most cases (90.6%), the results are confirmed between the 4th and 15th day after infection[55]. This analytical method involves reverse transcription of the genetic material obtained from respiratory secretions, specifically nasal samples[12]. The World Health Organization (WHO) has recommended that samples be collected from the upper respiratory tract soon after the onset of symptoms. RT-PCR tests have a specificity of 100% and a sensitivity of 64%, making them the gold standard for diagnosis[56].

Another method for rapid diagnosis is the identification of IgG and IgM antibodies using immunoassay techniques. However, this method has been discouraged by the WHO due to its lack of sensitivity and specificity[12]. Serological test kits become important when investigating the spread of COVID-19, but this can be challenging due to cross-reactivity of antibodies[56].

Biochemical tests have been found to be good predictors of the prognosis of the disease. Elevated levels of biomarkers such as lactate dehydrogenase, C-reactive protein, ferritin, D-dimer, lymphopenia, thrombocytopenia, renal and hepatic dysfunction, and increased levels of cytokines such as IL-6 and other interleukins have been observed in studies[12].

Elevation of troponin is associated with increased risk of in-hospital mortality and adverse outcomes in patients with COVID-19. Cardiovascular care teams should have a high index of suspicion for fulminant presentations resembling positive myocarditis[57].

Final considerations

The first studies have found that SARS-CoV-2 has a spherical shape composed of a glycoprotein matrix with a diameter ranging from 60 to 160 nm. Inside, it contains a single-stranded positive-sense RNA viral genome belonging to the beta-coronavirus genotype.

Research on COVID-19 has shown that the disease can be transmitted in three ways: first, through person-to-person transmission via respiratory droplets in enclosed environments; second, through circulating aerosols in the environment; and third, through physical contact with contaminated surfaces. The incubation period of the disease can last up to 27 days, as reported by some authors, but in 97.5% of infected individuals, symptoms appear within 11.5 days after exposure.

Hypotheses presented in scientific publications about the pathogenicity of SARS-CoV-2 in the host consist of three stages: Inoculation, pneumonia, and systemic hyperinflammation. People diagnosed with COVID-19 can develop the following clinical presentations: asymptomatic, mild, moderate, severe, and critical.

Signs and symptoms related to a mild clinical presentation are very similar to those of a common cold or flu, such as fever, fatigue, cough, headache, sore throat, runny nose, sneezing, nausea, vomiting, diarrhea, and abdominal pain. In the moderate presentation, there is pneumonia without hypoxia, while in the severe presentation, pneumonia with hypoxia is present. In the critical clinical presentation, the patient exhibits symptoms of acute respiratory distress syndrome, shock, encephalopathy, myocarditis, heart failure, as well as blood coagulation dysfunction and acute kidney injury. The progression of the disease's clinical course has been associated with the presence of comorbidities such as hypertension, diabetes, cancer, pre-existing respiratory failure, and obesity. Obesity stood out with 48.3% of severe cases. However, it is considered that the majority (60-80%) of cases are asymptomatic, which implies an imperceptible acceleration of transmission.

The gold standard test for diagnosis was the reverse transcription-polymerase chain reaction (RT-PCR) immunoenzymatic assay. Other tests such as immunological assays (rapid antibody tests), imaging exams, and biochemical tests were used to confirm clinical outcomes and prognosis.

Despite numerous studies published in the first year of the COVID-19 pandemic, there are still gaps in understanding its pathophysiological process, including the long-term consequences of this disease. Therefore, further research on this morbidity and its consequences is needed. Finally, this review acknowledges the undeniable advancements of science, which, within a year, has sought to generate knowledge to tackle the COVID-19 pandemic.

Conflict of interests

The authors declare that there is no potential conflict of interest.

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References

1. Guo G, Ye L, Pan K, Chen Y, Xing D, Yan K, et al. New Insights of Emerging SARS-CoV-2: Epidemiology, Etiology, Clinical Features, Clinical Treatment, and Prevention. Front Cell Dev Biol. 2020;8(May):1–22.
2. Garcia LP, Duarte E. Intervenções não farmacológicas para o enfrentamento à epidemia da COVID-19 no Brasil. Epidemiol e Serv saude Rev do Sist Unico Saude do Bras. 2020;29(2):e2020222.
3. OMS. Novel Coronavirus(2019-nCoV). Who. 2020;(January).
4. Bender JB, Hueston W, Osterholm M. Recent animal disease outbreaks and their impact on human populations. J Agromedicine. 2006;11(1):5–15.

5. Domingues L. Infodemia: uma ameaça à saúde pública global durante e após a pandemia de Covid-19. Rev Eletrônica Comun Informação e Inovação em Saúde. 2021;15(1):12–7.

6. Falcão P, Souza AB de. Pandemia de desinformação: as fake news no contexto da Covid-19 no Brasil. Rev Eletrônica Comun Informação e Inovação em Saúde. 2021;15(1):55–71.

7. OMS. COVID-19 Strategic Preparedness and Response Plan - OPERATIONAL PLANNING GUIDELINES TO SUPPORT COUNTRY PREPAREDNESS AND RESPONSE [Internet]. Vol. 13, Who. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/covid-19-sprp-unct-guidelines.pdf

8. Mota de Sousa LM, Furtado Firmino C, Alves Marques-Vieira CM, Silva Pedro Severino S, Castelão Figueira Carlos Pestana H. Revisões da literatura científica: tipos, métodos e aplicações em enfermagem. Rev Port Enferm Reabil. 2018;1(1):45–55.

9. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199–207.

10. Bhat TA, Kalathil SG, Bogner PN, Blount BC, Goniewicz ML, Thanavala YM. An animal model of inhaled Vitamin E acetate and Evali-like lung injury. N Engl J Med. 2020;382(12):1175–7.

11. OMS. Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts. Who. 2020;(January):4–6.

12. Carvajal ACC De, Parra AR, Silano MF. Nuevo coronavirus (SARS-COV-2): una amenaza global. Med Interna (Bucur). 2020;36(1):3–15.

13. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC, Joost Wiersinga W. Pathophysiology, Transmission, Diagnosis, and Treatment ofCoronavirus Disease 2019 (COVID-19) AReview. JAMA [Internet]. 2020;324(8):782–93. Available from: https://jamanetwork.com/

14. Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. Int J Oral Sci. 2020;12(1):1–6.

15. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Emergence, transmission, and characteristics of human coronaviruses. J Adv Res [Internet]. 2020 Jul;24:91–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2090123220300540

16. Parra-Izquierdo V, Florez-Sarmiento C, Romero-Sanchez MC. Inducción de "tormenta de citocinas" en pacientes infectados con SARS- CoV-2 y desarrollo de COVID-19. ¿Tiene el tracto gastrointestinal alguna relación en la gravedad? Rev Colomb Gastroenterol. 2020;35(Supl. 1):21–9.

17. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients with Novel Coronavirus Disease 2019. Clin Infect Dis. 2020;71(16):2027–34.

18. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology : A review. Clin Immunol. 2020;215(April):1–8.

19. Market M, Angka L, Martel AB, Bastin D, Olanubi O, Tennakoon G, et al. Flattening the COVID-19 Curve With Natural Killer Cell Based Immunotherapies. Front Immunol. 2020;11(June):1–23.

20. Jain A, Doyle DJ. Stages or phenotypes? A critical look at COVID-19 pathophysiology. Intensive Care Med. 2020;46(7):1494–5.

21. Pérez A G, Cordero R C, Avendaño C LF. Otro Desafio De La Naturaleza: El Nuevo Coronavirus Virología Y Fisiopatología Del Sars-Cov-2. Neumol Pediátrica. 2020;15(2):301–7.

22. Xiao L, Sakagami H, Miwa N. ACE2: The key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: Demon or angel? Viruses. 2020;12(5):2002–3.

23. Steardo L, Zorec R, Verkhratsky A, Rocha VN, Xiao L, Sakagami H, et al. Otro Desafio De La Naturaleza: El Nuevo Coronavirus Virología Y Fisiopatología Del Sars-Cov-2. Front Med [Internet]. 2020;18(1):1–9. Available from: https://doi.org/10.1186/s12929-020-00703-5

24. Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging." Inflamm Res. 2020;69(9):825–39.

25. Ylikoski J, Markkanen M, Mäkitie A. Pathophysiology of the COVID-19–entry to the CNS through the nose. Acta Otolaryngol. 2020;140(10):886–9.

26. Kasal DA, Lorenzo A de, Tibiriçá E. COVID-19 and Microvascular Disease: Pathophysiology of SARS-CoV-2 Infection With Focus on the Renin-Angiotensin System. Hear Lung Circ. 2020;29(January):1–8.

27. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: Why Children Fare Better than Adults? Indian J Pediatr. 2020;87(7):537–46.

28. OMS. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19: Scientific Brief 15 May 2020. Who [Internet]. 2020;10(May):1–9. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19%0Ahttp://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.

29. Das SK. The Pathophysiology, Diagnosis and Treatment of Corona Virus Disease 2019 (COVID-19). Indian J Clin Biochem. 2020;35(4):385–96.

30. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

31. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34(January).

32. Terceiro D, Vietto V. COVID-19 : Presentación clínica en adultos. EVIDENCIA. 2020;23:9–12.

33. Sepúlveda C V, Waissbluth A S, González G C. Anosmia y enfermedad por Coronavirus 2019 (COVID-19): ¿Qué debemos saber? Rev Otorrinolaringol y cirugía cabeza y cuello. 2020;80(2):247–58.

34. Tsatsakis A, Calina D, Falzone L, Petrakis D, Mitrut R, Siokas V, et al. SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. Food Chem Toxicol. 2020;146(September):111769.

35. Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G, Zeidman A, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. Clin Transl Med. 2020;10(2):3–7.

36. Shrestha GS, Khanal S, Sharma S, Nepal G. COVID-19: Current Understanding of Pathophysiology. J Nepal Health Res Counc. 2020;18(3):351–9.

37. Violetis OA, Chasouraki AM, Giannou AM, Baraboutis IG. COVID-19 Infection and Haematological Involvement: a Review of Epidemiology, Pathophysiology and Prognosis of Full Blood Count Findings. SN Compr Clin Med. 2020;2(8):1089–93.

38. Xing Y, Wang H, Yao XH, Li Y, Huang JT, Tang J, et al. Analysis of factors for disease progression in 61 patients with COVID-19 in Xiaogan, Hubei, China. Eur Rev Med Pharmacol Sci. 2020;24(23):12490–9.

39. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020;194(May):101–15.

40. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8(12):1201–8.

41. Barros BCS, Maia AB, Marques MA, Prette-Junior PR, Fiorelli SKA, Cerqueira FDC. The role of angiology and vascular surgery in the covid-19 pandemic. Rev Col Bras Cir. 2020;47(1):1–9.

42. Piazza G, Marrow DA. Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19. Clin Rev e Educ. 2020;18(8):1859–65.

43. Tu TM, Goh C, Tan YK, Leow AS, Pang YZ, Chien J, et al. Cerebral Venous Thrombosis in Patients with COVID-19 Infection: a Case Series and Systematic Review. J Stroke Cerebrovasc Dis. 2020;29(12):1–9.

44. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, et al. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Hear Rhythm. 2020;17(9):1463–71.

45. Petrovic V, Radenkovic D, Radenkovic G, Djordjevic V, Banach M. Pathophysiology of Cardiovascular Complications in COVID-19. Front Physiol. 2020;11(October):1–11.

46. Sabioni L, De Lorenzo A, Lamas C, Muccillo F, Castro-Faria-Neto HC, Estato V, et al. Systemic microvascular endothelial dysfunction and disease severity in COVID-19 patients: Evaluation by laser Doppler perfusion monitoring and cytokine/chemokine analysis. Microvasc Res [Internet]. 2021;134(November 2020):104119. Available from: https://doi.org/10.1016/j.mvr.2020.104119

47. Asgharpour M, Zare E, Mubarak M, Alirezaei A. COVID-19 and Kidney Disease: Update on epidemiology, clinical manifestations, pathophysiology and management. J Coll Physicians Surg Pakistan. 2020;30(1):S19–25.

48. Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, et al. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Rev Med Virol. 2020;(September):1–13.

49. Ng JH, Bijol V, Sparks MA, Sise ME, Izzedine H, Jhaveri KD. Pathophysiology and Pathology of Acute Kidney Injury in Patients With COVID-19. Adv Chronic Kidney Dis. 2020;27(5):365–76.

50. Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol. 2020;229(3):10–3.

51. Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-Cov-2 Infection: Pathophysiology and Clinical Effects on the Nervous System. World Neurosurg. 2020 Aug;140(1):49–53.

52. Yu H, Sun T, Feng J. Complications and Pathophysiology of COVID-19 in the Nervous System. Front Neurol. 2020;11(December):1–8.

53. Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J. 2020;1(1):1–9.

54. Rafiee F, Keshavarz P, Katal S, Assadi M, Nejati SF, Ebrahimian Sadabad F, et al. Coronavirus Disease 2019 (COVID-19) in Molecular Imaging: A Systematic Review of Incidental Detection of SARS-CoV-2 Pneumonia on PET Studies. Semin Nucl Med. 2021;51(2):178–91.

55. Liu Z, Ding L, Chen G, Zhao C, Luo X, Li X, et al. Clinical Time Features and Chest Imaging of 85 Patients With COVID-19 in Zhuhai, China. Front Med. 2020;7(February):1–10.

56. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review. J Med Virol. 2020;93(1):275–99.

57. Levett JY, Raparelli V, Mardigyan V, Eisenberg MJ. Cardiovascular Pathophysiology, Epidemiology, and Treatment Considerations of Coronavirus Disease 2019 (COVID-19): A Review. CJC Open. 2020;3(1):28–40.