Coronavirus Disease 2019: Clinical Review

Doença de Coronavírus 2019: Revisão Clínica

Cristina Carvalho GOUVEIA✉[1], Luís CAMPOS[1]
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ABSTRACT

Introduction: In December 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, the capital of Central China's Hubei Province and has been declared a public health emergency of international concern by the World Health Organization since January 2020.

Material and Methods: A comprehensive search using the PubMed database was carried out to summarize the latest published information about the epidemiology, definition, pathogenesis, clinical characteristics, treatment options, prognosis and prevention of coronavirus disease 2019.

Discussion: This new strain of coronavirus, named severe acute respiratory syndrome coronavirus 2, enters human cells that express angiotensin-converting enzyme II receptors, which exist in the respiratory, gastrointestinal and genitourinary tracts and heart, causing coronavirus disease. Transmission occurs essentially through the respiratory tract and the main symptoms are fever, cough and dyspnea. Diagnosis is based on epidemiological, clinical and imaging features and confirmed by nucleic acid testing.

Conclusion: Despite intensive research, the exact origin of the virus and pathophysiology of coronavirus disease is not yet completely known, and clinically approved vaccines and drugs that target severe acute respiratory syndrome coronavirus 2 are lacking.

Keywords: Coronavirus Infections; COVID-19; Severe Acute Respiratory Syndrome

RESUMO

Introdução: Em dezembro de 2019, ocorreu um surto de pneumonia causada por uma nova estirpe de coronavírus em Wuhan, a capital da província de Hubei, na China central e foi declarado emergência de saúde pública de âmbito internacional pela Organização Mundial de Saúde, em janeiro de 2020.

Material e Métodos: Foi realizada uma pesquisa na base de dados PubMed, de forma a sintetizar a informação mais recentemente publicada sobre a epidemiologia, definição, fisiopatologia, manifestações clínicas, tratamento, prognóstico e prevenção da doença de coronavírus 2019.

Discussão: Esta nova estirpe de coronavírus, denominada coronavírus da síndrome respiratória aguda grave 2 infeta células que expressem o recetor da enzima conversora da angiotensina tipo II, existentes nos tratos respiratório, gastrointestinal e geniturinário e no coração, provocando a doença de coronavírus 2019. A transmissão ocorre essencialmente através do trato respiratório e os principais sintomas são febre, tosse e dispneia. O diagnóstico é baseado em critérios epidemiológicos, clínicos e imagiológicos, sendo a confirmação da doença realizada através da análise de ácidos nucleicos.

Conclusão: Apesar da extensa investigação, ainda não é totalmente conhecida a origem do vírus, a fisiopatologia da doença e não existem vacinas nem tratamento direcionados a esta nova estirpe de coronavírus.

Palavras-chave: COVID-19; Infecções por Coronavírus; Síndrome Respiratória Aguda Grave

INTRODUCTION

Coronaviruses are a common source of upper respiratory, enteric, hepatic and central nervous system infections in humans.[1,2] Two strains of coronavirus, namely SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) were responsible for respiratory disease outbreaks, in 2002 - 2003 and 2012 - 2013, respectively.[3] Recently, a new strain, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in China and has been responsible for the coronavirus disease 2019 (COVID-19) pandemic.[4] As of 25th May 2020, a total of 5 304 772 cases of SARS-CoV-2 infection have been confirmed in the world, including 342 029 deaths.[5] In Portugal, on this date, 30 788 people have been infected by the novel coronavirus and 1330 have died because of COVID-19.[6]

MATERIAL AND METHODS

A comprehensive search using PubMed database was performed using the terms 'COVID', 'COVID-19' and 'SARS-CoV-2'. After investigation and selection, 68 articles, which included original and review articles were comprised, based on their relevance. One of the articles used was published in 2019 and the rest were published in their definitive version of ahead of print in 2020. The websites of the World Health Organization (WHO) and Direção-Geral da Saúde (DGS) were consulted on 26th May 2020 for updated epidemiological data.

DISCUSSION

Epidemiology and origin

After the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), China developed a 'pneumonia of unknown etiology' surveillance mechanism, which allowed the identification of the first cases, in December 2019.[7] Because the majority of the earliest cases were linked to a seafood and

1. Departamento de Medicina Interna. Hospital de São Francisco Xavier. Lisboa. Portugal.
✉ Autor correspondente: Cristina Carvalho Gouveia. cristinamarisa@campus.ul.pt
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wet animal wholesale market in Wuhan, China, a zoonotic or environmental way of exposure was suggested.[2,7,8] Although there is no consistent evidence that the virus originated in the market, it is suggested that bats were involved in the origin of SARS-CoV-2.[9,10] Bats are the reservoir of various coronaviruses and SARS-CoV-2 shares a 96.2% genetic identity to a bat SARS-related coronavirus, namely SARSr-Ra-Bat-CoV-RaTG13.[9] Additionally, the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein seems to be a mutation of the aforementioned bat coronavirus RaTG13.[11] Therefore, current evidence supports that SARS-CoV-2 originated from bats and gained the ability of infecting other animals through mutation.[11] Consequently, the first transmission would have occurred between bats and an undetermined intermediate host animal.[12] It is hypothesized that SARS-CoV-2 originated from a recombination event between RaTG13 and the strain of coronavirus found in pangolins, which means that the pangolin might be the intermediate host.[13,14] However, snakes and turtles are also being investigated as potential intermediate hosts.[15] Direct contact or consumption of these animals may have been the main route of SARS-CoV-2 transmission.[16] Additional studies are necessary to confirm the origin of SARS-CoV-2, in order to avoid zoonotic transmission and prevent future disease outbreaks.[14]

Currently, there is also evidence of human-to-human transmission, mainly between close contacts and healthcare workers.[16] Epidemiological data reported 5.2 days as the mean incubation period of COVID-19.[17] The mean serial interval of COVID-19 is 7.5 days, and, currently, the period for medical observation is 14 days (the serial interval is the period between illness onset in a primary case and disease onset in the secondary case).[17] The Reproductive number (R_0) is the average number of additional infections that an infectious person can generate, representing the transmissibility of a virus.[17] Generally, an R_0 higher than 1 means that the epidemic will continue to increase. R_0 of SARS-CoV-2 is estimated to be 3.28, as opposed to 3 and < 1 of SARS and MERS, respectively.[17,18]

Definition and etiology

Coronaviruses are enveloped, single positive stranded ribonucleic acid (RNA) viruses, belonging to the beta coronavirus genus.[19] After the announcement of an outbreak of pneumonia of unknown etiology, in late December, SARS-CoV-2 was identified as the causative agent, in January 2020.[7] This coronavirus strain was first identified in the bronchoalveolar-lavage fluid of three patients with COVID-19 who were hospitalized in Wuhan.[20] Given the genetic similarity between the novel coronavirus and two SARS-like CoV sequences isolated in bats between 2015 to 2017, it was considered a SARS-like virus and was named SARS-CoV-2.[2,21] This novel coronavirus is the seventh member of coronaviruses that infects humans and shares 79.5% and 50% genetic identity to SARS-CoV and MERS-CoV, respectively.[9,22]

Pathogenesis

Viral characteristics and infection capacity

The RNA of coronaviruses encodes several non-structure proteins (NSPs) and four structural proteins, namely spike surface glycoprotein (S), envelope (E), membrane (M) and nucleocapsid (N) proteins.[23] The viral spike protein of coronaviruses recognizes and binds to various host receptors in human cells, including angiotensin-converting enzyme II (ACE2) and dipeptidyl peptidase 4 (DPP4).[24] SARS-CoV contains a variable receptor-binding domain, that binds to ACE2 host cell receptors, allowing viral entry into cells.[9] Zhou *et al* demonstrated, through bronchoalveolar lavage fluid examination, that SARS-CoV-2 uses the same cell receptor as SARS-CoV.[25] Moreover, Wrapp *et al* demonstrated that SARS-CoV-2 has higher affinity to ACE2 than SARS-CoV, which may facilitate human-to-human transmission.[26] Because receptor recognition by coronaviruses is an important determinant of viral infectivity and pathogenesis, it represents a major target for vaccination and treatment strategies.[16,27,28]

SARS-CoV-2 was first identified in the bronchoalveolar-lavage fluid and it is presumed that primary viral replication occurs in the upper respiratory tract (nasal and pharynx mucosa) with additional viral multiplication in the lower respiratory tract.[20,24] In the lungs, binding of the virus to the type II pneumocytes is associated with dysfunction of renin-angiotensin system, resulting in altered pulmonary vascular permeability and pulmonary edema.[24] The alveolar damage combined with a pro-inflammatory state lead to the development of severe acute respiratory syndrome.[11,16,22] However, COVID-19 is associated with dysfunction of other organs, such as the heart, kidney and liver.[29,30] The fact that ACE2 is expressed in the nasal mucosa, bronchus, lung, heart, esophagus, stomach, intestine, kidney, bladder and testicles suggests that all these organs may be vulnerable to SARS-CoV-2.[11,24,31]

The N protein of SARS-CoV is essential for virus transcription and assembly efficiency.[2] Mutations in protein domains may improve viral pathogenicity and capacity of infection.[2] Angeletti *et al* reported that mutations in NSP2 and NSP3 proteins could be responsible for the infectious ability of SARS-CoV-2 and differentiation mechanism from SARS.[32]

Immunopathology

The immune system is essential for control of the SARS-CoV-2 infection.[16] However, excessive immune responses may be responsible for worse clinical outcomes.[16,33]

Wang *et al* demonstrated impairment of the immune system of patients with COVID-19, by reporting lymphopenia and decreased levels of CD4+, CD8+, B and natural killer (NK) cells in these patients.[34] COVID-19 is also associated with a cytokine storm, characterized by release of pro-inflammatory cytokines, chemokines and biomarkers such as interleukins 2, 6, 7 and 8 (IL-2, IL-6, IL-7 and IL-8), tumor necrosis factor alpha (TNF-α) and granulocyte-colony stimulating factor.[33,35] Infection by SARS-CoV-2 also

results in increased inflammatory markers, such as C-reactive protein (CRP), ferritin and D-dimer and destruction of the immune system, demonstrated by atrophy of the spleen and lymph nodes.[33,36] It has been demonstrated that severe disease is associated with higher level of pro-inflammatory parameters and cytokines (IL-6, IL-1β, IL2R, IL-8 and TNF-α, CRP, ferritin, D-dimer) and lower levels of T cells.[33] Troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) can also be elevated in these patients.[35] In fact, CD8+ T cells were suggested as an independent predictor for COVID-19 severity and treatment efficacy.[34] The importance of the immune system in COVID-19 severity has been subject of research and treatment options that target these mechanisms have been proposed.[33]

Disease course

The pathophysiology of COVID-19 seems to be the result of two mechanisms: one triggered by the virus and the other represented by the host response.[35]

Siddiqi *et al* proposed the staging of COVID-19 in three phases: stage I (early infection), II (pulmonary involvement) and III (systemic hyperinflammation).[35] Stage I represents mild disease, and comprises the incubation period, absence of symptoms and the presence of mild symptoms, such as malaise, fever and dry cough and the presence of lymphopenia.[35] Stage II (moderate disease) is characterized by lung involvement and can be divided in stage IIa (without hypoxia) and IIb (with hypoxia). In this stage, laboratory tests may show lymphopenia, elevated transaminases and chest imaging demonstrate bilateral pulmonary infiltrates. In stage II, patients normally require hospitalization, supportive treatment and antiviral medication should be considered.[35] An extra-pulmonary systemic hyperinflammatory syndrome represents the stage III of COVID-19.[35] This stage is characterized by elevation of inflammatory cytokines and biomarkers and a secondary haemophagocytic lymphohistiocytosis, manifested by fever, cytopenia and hyperferritinaemia.[36] The systemic inflammation may justify the use of immunomodulatory agents in this stage.[35]

Transmission mechanisms

SARS-CoV-2 is essentially transmitted through the respiratory tract, by droplets, respiratory secretions and direct contact with the oral or nasal mucosa.[16,37] Therefore, the virus can be detected in oral and nasal swabs.[16,37] Transmission via ocular surfaces may be a possibility, through human conjunctival epithelium contamination by droplets and other body fluids.[38] Zhang *et al* proposed that the considerable expression of ACE2 in the esophagus, ileum and colon may indicate that the digestive tract is as an alternative and potential route of infection.[1] Guan *et al* detected SARS-CoV-2 in gastrointestinal tract specimens, namely in stool and rectal swabs and, in patients with severe peptic ulcer disease, in esophageal erosion and bleeding sites.[39] They also reported SARS-CoV-2 in saliva and urine samples.[39] Zhang *et al* detected the virus in anal swabs and blood and reported that these specimens may be positive even when the oral swab is negative.[40] These observations suggest fecal-oral and body fluids as alternatives routes of transmission.[40] Although this hypothesis is yet to be confirmed, testing of faecal and urine samples has been recommended to exclude alternative routes of transmission.[8]

Diagnostic features

Clinical manifestations

The diagnosis of COVID-19 is based on epidemiological history, clinical manifestations and laboratory tests.[29]

Rodriguez-Morales *et al* reported fever, cough and dyspnea as the most prevalent symptoms.[10] Other clinical manifestations include: myalgia, fatigue, sputum production, sore throat, rhinorrhea, headache, dizziness and hemoptysis.[10,22,29] Tian *et al* concluded that gastrointestinal symptoms occur in 3% - 79% of cases and include anorexia, diarrhea, vomiting, nausea, abdominal pain and gastrointestinal bleeding.[19] Fan *et al* suggested that testicular tissue damage induced by SARS-CoV-2 might result in male infertility.[41] It is important to note that patients may be asymptomatic or present with digestive symptoms in the absence of respiratory symptoms.[19,42]

According to Rodriguez-Morales *et al*, the most common laboratory findings are decreased albumin, high C-reactive protein (CRP), lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR) and lymphopenia.[10] Other laboratory abnormalities include: thrombocytopenia, leukopenia, leukocytosis and elevated transaminases, bilirubin, urea, creatinine and D-dimer.[10]

Complications associated with COVID-19 include acute respiratory distress syndrome, RNAaemia (positive result for real-time reverse transcription polymerase chain reaction in the plasma sample), acute cardiac, liver and kidney injury, arrhythmia, coagulation dysfunction, shock, secondary infections and multiple organ failure.[29,30]

Imaging studies

Because of the primary involvement of the respiratory system in COVID-19, chest imaging is used for initial evaluation and follow-up of patients.[43]

Chest radiography can be used for diagnosis, evaluation of complications and follow-up of patients.[43] Rodriguez-Morales *et al* reported bilateral pneumonia as the most common finding on chest-X-rays.[10]

Chest computed tomography (CT) has higher sensitivity than chest radiography in identifying manifestations of COVID-19 and can be used to stratify patients and assist in diagnosis and treatment decisions in patients with unclear scenarios or comorbidities.[44] Although CT may be abnormal even before symptom onset, it has limited sensitivity and negative predictive value in the first two days after symptom onset and, therefore, should not be used alone to rule out COVID-19.[43,45]

The typical findings of COVID-19 pneumonia in CT include peripheral and/or posterior bilateral ground-grass opacities and patchy consolidations, mainly in the subpleural area, that increase and extend to the middle and

outer zones of the lung as disease progresses.[43,46,47] The most severe CT findings generally occur ten days after symptom onset and consist of diffuse lesions and a 'white lung' appearance.[47] CT signs of clinical improvement usually appear after two weeks of disease and manifest as resolution of the lesions, although a fibrous stripe may be apparent.[47] Other less common findings include septal thickening, bronchiectasis, pleural and pericardial effusion and pneumothorax.[43] Solid pulmonary nodules, cavitation and lymph node enlargement are not typical findings of COVID-19.[46]

Laboratory tests

Currently, the gold standard method for detection of SARS-CoV-2 is nucleic acid testing by reverse transcription polymerase chain reaction (RT-PCR) using respiratory samples.[12] Upper respiratory samples include nasopharyngeal and oropharyngeal swabs, nasopharyngeal washes and nasal aspirates while sputum, bronchoalveolar lavage and tracheal aspirates represent lower respiratory tract samples.[12] Yang *et al* compared the sensitivity of sputum, nasal and oral swabs for detection of SARS-CoV-2 and demonstrated that sputum was the most reliable sample, followed by the nasal swab.[48]

Because RT-PCR of viral nucleic acid has limited sensitivity (60-70%), the search for new testing methods is currently evolving.[44] Yu *et al* compared RT-PCR with ddPCR (droplet digital PCR) and reported that the latter was more useful in detecting the virus in samples with lower viral loads.[49] Zhao *et al* detected the appearance of total antibodies, immunoglobulin M (IgM) and immunoglobulin G (IgG) against SARS-CoV-2 with a median seroconversion time of 11, 12 and 14 days, respectively.[50] The use of serological tests in conjunction with nucleic acid testing has been suggested in order to improve the sensitivity of the COVID-19 diagnosis.[50]

Treatment

There are currently no specific treatments or vaccines for COVID-19.[24] The treatments that have been used against SARS-CoV-2 are based on their effectiveness on SARS-CoV, MERS-CoV and other previous strains of coronavirus.[51]

The treatment options currently available include hydroxychloroquine, macrolides, nucleoside analogues and anti-inflammatory medications.[8]

Chloroquine and hydroxychloroquine have immunomodulatory and anti-inflammatory effects.[33] *In vitro* studies reported that chloroquine can inhibit SARS-CoV-2 infection.[52] The mechanism of action against SARS-CoV-2 involves the inhibition of viral binding to cell receptors, viral cycle and maturation of viral proteins.[33,53] Additionally, they affect cell signaling and production of pro-inflammatory cytokines.[33,54] The first available clinical studies showed promising results regarding the use of these medications in COVID-19.[52,55] However, the existence of considerable methodological problems in these studies has questioned the actual role of hydroxychloroquine and chloroquine in COVID-19.[56,57] Additionally, the doses of hydroxychloroquine recommended for COVID-19 are higher than those generally used for chronic conditions and can be associated with potentially fatal cardiac toxicity.[56,57] Therefore, although *in vitro* experiments suggest that these medications may have a role in COVID-19 treatment, current clinical evidence does not support their use in this disease.[56]

Macrolides have anti-bacterial activity and immunomodulatory and anti-inflammatory effects.[58] Gautret *et al* reported that hydroxychloroquine treatment for COVID-19 patients was associated with viral clearance and that this effect was reinforced by co-administration of azithromycin.[55] However, this study had several limitations, such as the small sample size and limited follow-up of patients.[55] Moreover, hydroxychloroquine and azithromycin are independently associated with QT interval prolongation and torsade de pointes and, therefore, should be used judiciously.[57]

Remdesivir is a nucleoside analogue with extensive antiviral activity that can inhibit the replication of several coronaviruses in the respiratory tract.[31] This drug inhibited SARS-CoV-2 infection in a human cell line *in vitro*.[59] However, the effectiveness and safety of remdesivir have not been established in clinical trials.[24,57]

Favipiravir is an RNA-dependent RNA polymerase inhibitor that may have potential activity against SARS-CoV-2, however, additional studies are necessary before it can be recommended as treatment for COVID-19.[60]

Lopinavir is a protease inhibitor that showed inhibitory capacity against SARS-CoV *in vitro* and has been used in combination with ritonavir to increase its plasma half-life.[61] Cao *et al* conducted a study that showed no significant differences regarding time to clinical improvement, viral clearance or mortality rates between the group of patients with COVID-19 who received lopinavir-ritonavir and the one receiving standard care.[61] Current data show limited role for lopinavir-ritonavir and additional studies are necessary to support their use in COVID-19.[54]

Given the importance of the immune system in COVID-19 pathogenesis, several anti-inflammatory medications have been studied as treatment for this disease.[33]

Xu *et al* reported that tocilizumab, a recombinant human IL-6 monoclonal antibody, was associated with clinical and radiological improvement in patients with severe COVID-19, suggesting that this drug may be a therapeutic strategy for this disease.[62]

Convalescent plasma or hyperimmune immunoglobulins could be used as adjunctive treatment, given that antibodies from recovered patients may help viral clearance in infected people.[54] Additionally, intravenous immune globulin (IVIG) may be useful in the hyperinflammatory state.[33]

No consensus has been reached regarding the use of glucocorticoids in COVID-19.[33] Generally, corticosteroids are not recommended in the treatment of COVID-19 because they may delay elimination of the virus and increase the risk of secondary infection.[33,54] However, it has been suggested that this medication may be beneficial in hyperinflammation immunosuppression and can also be

used in sepsis and septic shock, in a small dosage, after adequate fluids and vasopressor use.[33,36]

Caly *et al* demonstrated that ivermectin, an anti-parasitic agent that has been securely used in humans, had antiviral activity against SARS-CoV-2 *in vitro,* likely by inhibition of nuclear import of viral proteins.[63]

Antiviral drugs, such as the neuraminidase inhibitor oseltamivir, ganciclovir, acyclovir and ribavirin are not recommended for COVID-19.[16]

In conclusion, treatment of stage I is directed towards symptomatic relief, although antiviral medications such as hydroxychloroquine and remdesivir may be used, if proven beneficial, in all three disease stages.[35] In stage II, supportive measures are essential and, if mechanical ventilation is being considered, corticosteroids may be carefully used and immunomodulatory therapy, such as tocilizumab, pondered.[35] Immunomodulatory agents constitute the basis of stage III treatment, although corticosteroids and IVIG may be beneficial.[35]

Regarding coagulopathy associated with COVID-19, prophylactic anticoagulation with low molecular weight heparin (LMWH) is recommended to patients who require hospitalization for COVID-19, in the absence of contraindications.[64] Although D-dimer levels, sepsis and consumptive coagulopathy were associated with increased mortality, current evidence does not support the use of full dose anticoagulation unless otherwise clinically indicated, as is the case of atrial fibrillation and presence of mechanical cardiac valves.[65] LMWH and unfractionated heparin are preferred over direct oral anticoagulants, because of their shorter half-lives and parenteral administration.[65]

Prognosis

Around 80% of patients have mild symptoms and recover in one to two weeks.[24] The average mortality rate of SARS-CoV-2 globally, based on confirmed cases, is 3.8%, as opposed to 10% and 37.1% for SARS-CoV and MERS-CoV, respectively.[66] Development of respiratory failure from acute respiratory distress syndrome is the main cause of mortality in COVID-19.[36] The mean period from symptom onset to death is two weeks, ranging from 6 to 41 days.[8]

Older age and the presence of comorbidities, such as hypertension, diabetes, cardiovascular and respiratory tract diseases, cancer, smoking and obesity are associated with worse clinical outcomes.[24,67] Mo *et al* reported that older age, male sex, higher level of neutrophils, aspartate aminotransferase, LDH, CRP, lower level of platelets and albumin and presence of bilateral pneumonia and pleural effusion were associated with refractory COVID-19.[68] Ruan *et al* conducted a study that concluded that older age, presence of comorbidities (especially cardiovascular disease), secondary infection and elevated inflammatory indicators (cardiac troponin, myoglobin, CRP and IL-6) were predictors of mortality.[69] Additionally, endothelial damage caused by SARS-CoV-2, which may result in hypercoagulability, disseminated intravascular coagulation, anti-phospholipid syndrome and mimicry of vasculitis, is associated with worse prognosis.[33]

Prevention

It is known that coronavirus can survive for nine days on inanimate surfaces such as plastic or metal and, therefore, the use of ethanol and sodium hypochlorite is recommended to clean them.[11] Protective measures, such as personal hygiene, use of medical masks and room ventilation are also indicated to prevent infection and transmission of SARS-CoV-2.[22] Social distancing, isolation, quarantine at home and closure of several establishments such as schools, universities and work places are additional measures to prevent further spreading of infection.[70] Early reporting of SARS-CoV-2 infection and prompt isolation, diagnosis and management of patients are essential to reduce mortality and prevent further COVID-19 spreading.[39] Healthcare workers should use N95 / FFP grade respirators, protective suits and goggles / face shields and take precautions in procedures such as endotracheal and suction to avoid airborne transmission of SARS-CoV-2.[4] However, one of the biggest challenges in controlling COVID-19 spreading is that asymptomatic infected people and patients in the incubation period or recovered from COVID-19 may still transmit the infection to other people.[3,24] Additionally, because of the limited sensitivity of nucleic acid testing for COVID-19 diagnosis, patients who are infected may have a negative result and, therefore, contribute to disease spreading by not complying the appropriate measures to prevent COVID-19 transmission.[44]

CONCLUSION

The COVID-19 pandemic represents a tremendous challenge to healthcare systems all over the world. Because the causative agent, SARS-CoV-2 was discovered this year, its characteristics, mechanism of action and effect in humans were indefinite. Intensive research and sharing of clinical experience between healthcare professionals and scientists have been essential to expand the knowledge about the virus and COVID-19. However, despite intensive research, many questions remain unanswered. Current evidence supports that SARS-CoV-2 originated from an event of genomic recombination between two strains of coronavirus found in bats and pangolins and that it enters human cells through ACE2 receptors, found in the lungs, heart, kidney, bladder, testicles and the gastrointestinal tract. SARS-CoV-2 is transmitted through the respiratory tract and COVID-19 is essentially a respiratory disease, characterized by fever, cough, dyspnea and pneumonia on chest imaging. However, reports of additional symptoms and identification of SARS-CoV-2 in the gastrointestinal tract, feces, urine and blood raise the possibility of additional target organs and the existence of alternative routes of transmission. While the elderly and people with comorbidities are more susceptible to COVID-19 and have worse clinical outcome, additional data is necessary to define a patient's prognosis. Despite intensive research, there is currently no specific treatment for COVID-19. The existence of a hyperinflam-

matory response indicates that anti-inflammatory and immunomodulatory drugs may be essential. The identification of the molecular mechanism of viral entry and replication is a priority, in order to develop drugs and vaccines that target SARS-CoV-2.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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